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THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON RADICAL, SELENIUM, AND INOSITOL CHEMISTRY

by

MAARTEN H. D. POSTEMA ©

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
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For Rudolf and Jeannine

ABSTRACT

This thesis reports the results of three projects:

1 The development of a procedure for the ozonolytic cleavage of carbon-carbon double bonds in the presence of phenylseleno groups elsewhere in the substrate. The procedure entails oxidative cleavage of the olefin followed by reduction of both the formed ozonide and selenoxide by triphenylphosphine to the corresponding carbonyl compound and selenide, respectively. Such a procedure extends the utility of the phenylseleno group because it had hitherto been introduced only *after* double bond cleavage operations. My experiments have shown that this restriction is unnecessary.

2 The discovery of a method for carrying out radical cyclizations onto the carbonyl group of an aldehyde function. The procedure involved the use of triethylborane mediated 6-*exo* radical cyclization onto an aldehyde group. This procedure was used to construct bicyclic compounds with *trans* ring fusion. Closure onto an aldehyde had been observed previously, but only under special and synthetically limited conditions. The present methodology removes such restrictions.

3 Synthetic work aimed at the synthesis of *myo*-inositol 1,4,5-triphosphate by a method that involves an intramolecular ene reaction with a substrate that was built up from D-glucose.

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LIST OF ABBREVIATIONS

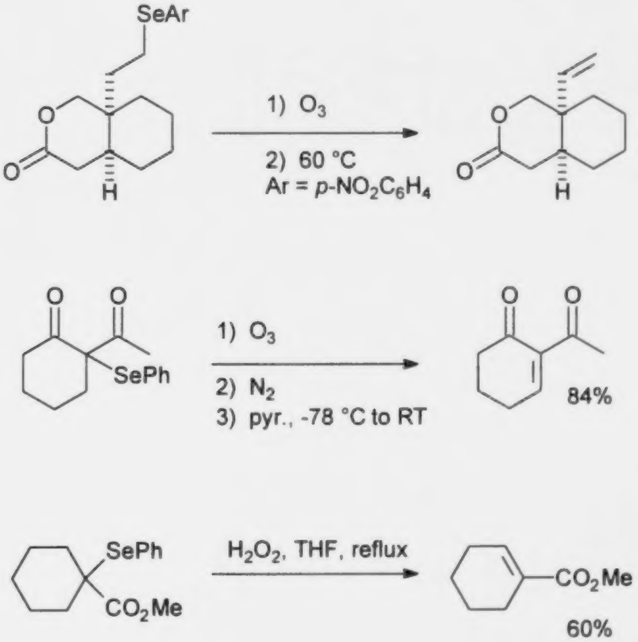
APT	Attached Proton Test
AIBN	azobisisobutyronitrile
Bn	benzyl
DABCO	1,4-diazobicyclo[2.2.2]octane
DIBAL	diisobutylaluminum hydride
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Imid	imidazole
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
NMO	4-methylmorpholine *N*-oxide
Ph	phenyl
Pmb	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
TBS or TBDMS	tert-butyldimethylsilyl
TMS	trimethylsilyl
Tr	triphenylmethyl

Chapter 1

Ozonolysis of Olefinic Phenyl Selenides with Preservation of the Selenium Unit: A Route to Phenylseleno Aldehydes and Ketones

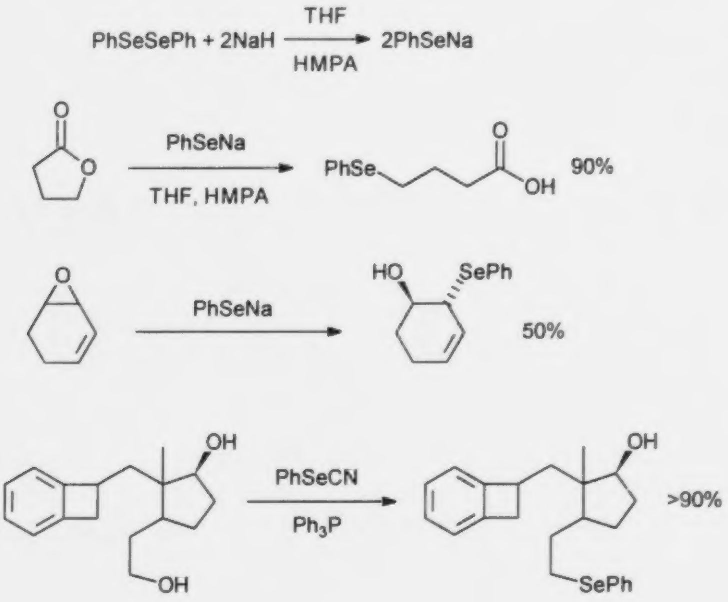
INTRODUCTION

The phenylseleno group occupies an important place in modern organic synthesis.[1] The main characteristics of the phenylseleno group (PhSe) are that it is sensitive to oxidation and is converted by a number of oxidizing procedures into the corresponding selenoxide.[2] This process constitutes an extremely efficient and exceptionally useful method for forming carbon-carbon double bonds, as the selenoxide collapses easily to an alkene, and its value is attested by the hundreds of examples that have appeared in the literature.[1] A few are shown in Scheme I-1.[3-5]


SeAr
O
O
H
1) O$_3$
2) 60 °C
Ar = p-NO$_2$C$_6$H$_4$
O
O
H
O
O
SePh
1) O$_3$
2) N$_2$
3) pyr., -78 °C to RT
O
O
84%
SePh
CO$_2$Me
H$_2$O$_2$, THF, reflux
CO$_2$Me
60%

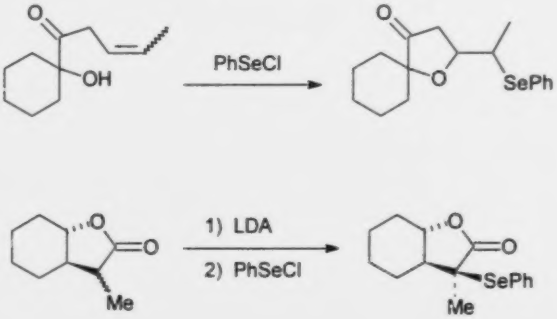
Scheme I-1

The general applicability of the phenylseleno group in organic synthesis relies on the ease of its introduction. Both nucleophilic and electrophilic selenium species have been developed. A few examples outlining the use of nucleophilic selenium are shown in Scheme I-2.[6-9]

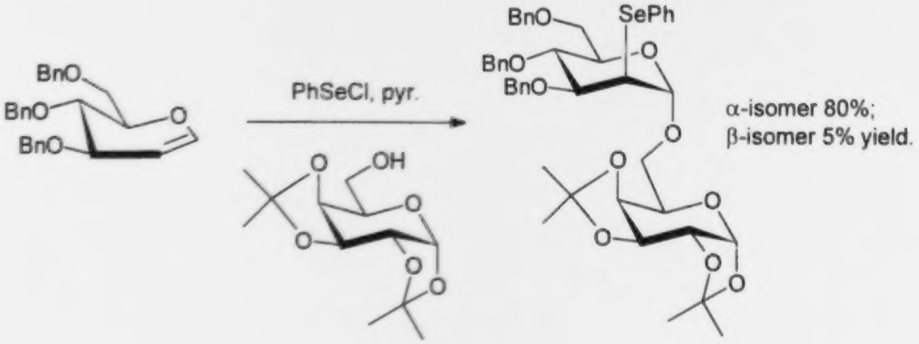

PhSeSePh + 2NaH
THF
HMPA
2PhSeNa
PhSeNa
THF, HMPA
PhSe
OH
90%
PhSeNa
HO
SePh
50%
OH
PhSeCN
Ph3P
OH
>90%
OH
SePh

Scheme I-2

The chemistry of electrophilic selenium is a very rich and fertile area, and representative examples of selenocyclization, α-selenation of ketones and alkoxy selenation of olefins are shown in Schemes I-3[10, 11] and I-4.[12]

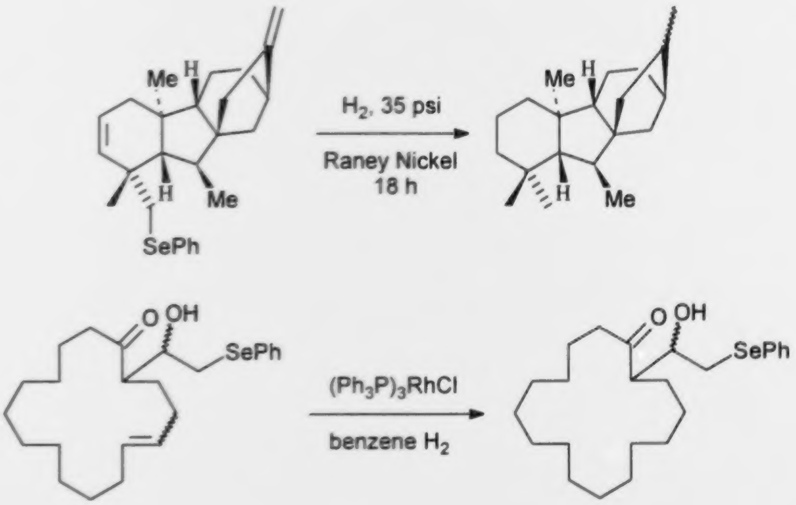

O
OH
PhSeCl
O
O
SePh
O
O
Me
1) LDA
2) PhSeCl
O
O
SePh
Me

Scheme I-3


BnO
BnO
BnO
PhSeCl, pyr.
OH
SePh
α-isomer 80%;
β-isomer 5% yield.

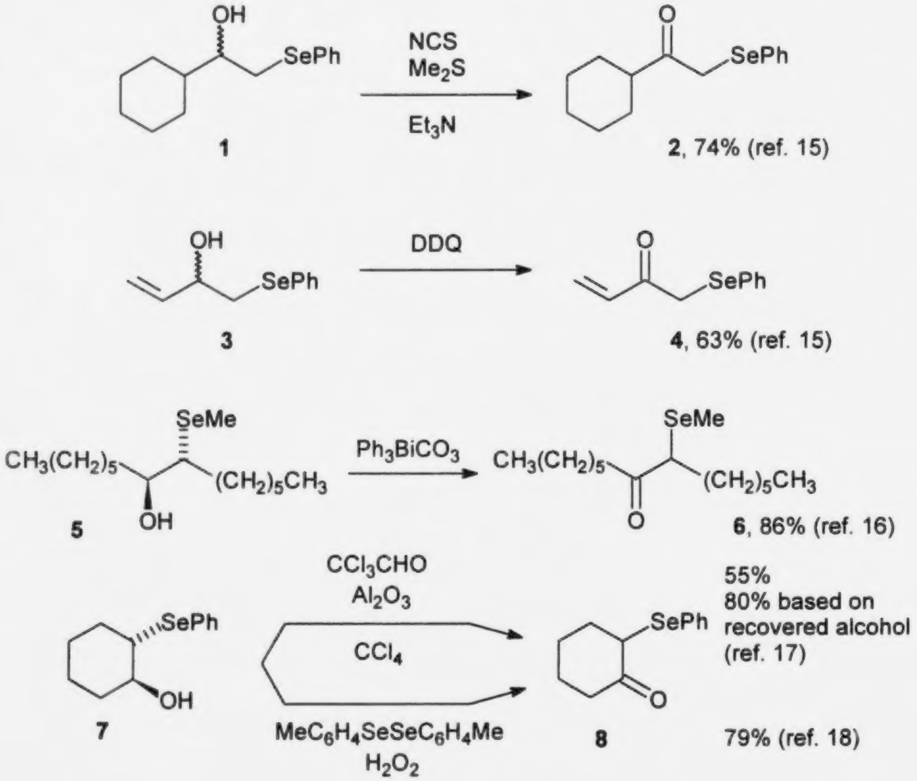
Scheme I-4

Another characteristic of the phenylseleno group is that it is not expected to survive hydrogenation conditions (H_2 Pd/C) and becausese of this expectation (based mainly on comparison with sulfur) there very few examples in the literature which involve hydrogenation processes of molecules containing the phenylseleno group. Those that are known to me are summarized in Scheme I-5.[13, 14]


Me
H
SePh
Me
H₂, 35 psi
Raney Nickel
18 h
SePh
(Ph₃P)₃RhCl
benzene H₂
SePh

Scheme I-5

For these reasons, although the phenylseleno group is important–particularly as a method of generating carbon-carbon double bonds–its introduction into a molecule has hitherto been timed after careful consideration of the subsequent reaction conditions to which the molecule would be exposed, while still having to retain the selenium function. In particular, oxidative conditions in the presence of the phenylseleno group are generally avoided. There a few exceptions to this though. It is known, for example, that alcohols containing the phenylseleno group, under carefully defined conditions listed in Scheme I-6, can be converted into


OH
SePh
NCS
Me$_2$S
Et$_3$N
1
O
SePh
2, 74% (ref. 15)
OH
SePh
DDQ
3
O
SePh
4, 63% (ref. 15)
SeMe
CH$_3$(CH$_2$)$_5$
(CH$_2$)$_5$CH$_3$
5
OH
Ph$_3$BiCO$_3$
SeMe
CH$_3$(CH$_2$)$_5$
(CH$_2$)$_5$CH$_3$
O
6, 86% (ref. 16)
CCl$_3$CHO
Al$_2$O$_3$
CCl$_4$
SePh
OH
7
MeC$_6$H$_4$SeSeC$_6$H$_4$Me
H$_2$O$_2$
SePh
O
8
55%
80% based on recovered alcohol (ref. 17)
79% (ref. 18)

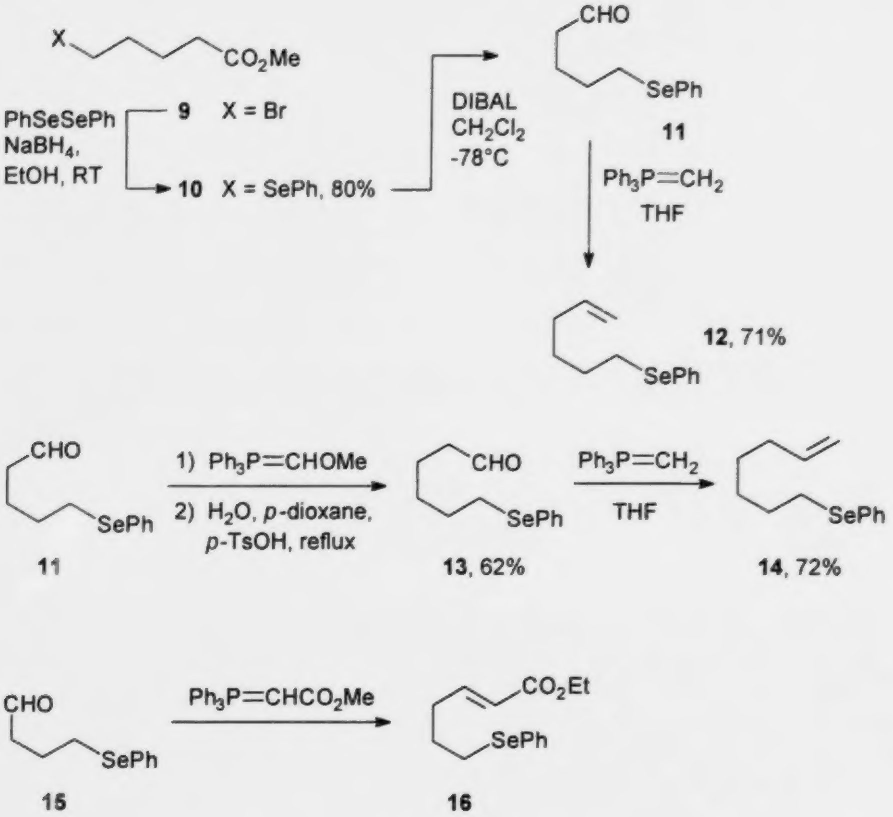
Scheme I-6

carbonyl compounds, but this procedure of alcohol oxidation is not often used.[15-18]

RESULTS and DISCUSSION

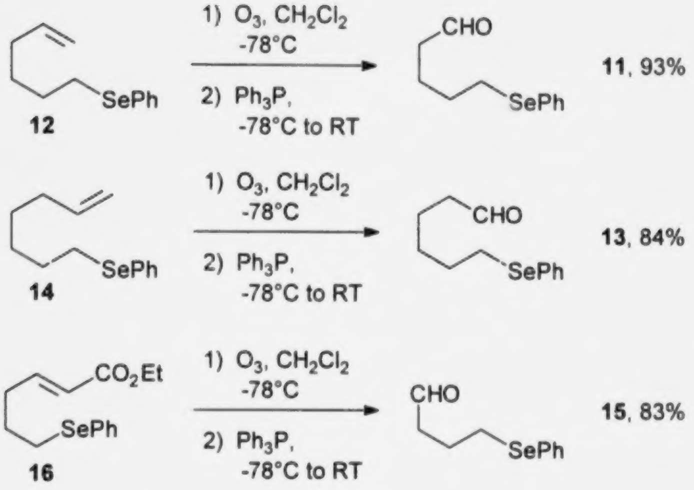
It has been known for a several years that the oxidation of selenides with ozone constitutes an effective method of making the selenoxide,[19] and hence the corresponding olefin.[1] Kinetic data[19] have shown that a phenylseleno group is oxidized much faster than a carbon-carbon double bond. However, it occurred to us that if an olefinic substrate containing a phenylseleno group were ozonized at a low temperature it may be possible to work up the reaction under such conditions that not only would the initial selenoxide (whose fragmentation we would anticipate to be slow at -78°C) be reduced back to the thermally stable selenide, but concomitant reduction of the ozonide or related species would also occur. If this were the case, then a phenylseleno group could be introduced in a synthetic sequence prior to the planned use of ozonolytic conditions. This would allow a much broader window of opportunity for the introduction of the phenyl selenide function.

We have studied a number of simple cases in which a carbon-carbon double bond and a phenylseleno group are present in the same molecule and have found that our speculations are indeed realized in practice. The olefinic selenides **12**, **15** and **16** were prepared by standard methods as shown in Scheme I-7.


X
CO2Me
PhSeSePh
NaBH4,
EtOH, RT
9 X = Br
10 X = SePh, 80%
DIBAL
CH2Cl2
-78°C
CHO
SePh
11
Ph3P=CH2
THF
SePh
12, 71%
CHO
SePh
11
1) Ph3P=CHOMe
2) H2O, p-dioxane, p-TsOH, reflux
CHO
SePh
13, 62%
Ph3P=CH2
THF
SePh
14, 72%
CHO
SePh
15
Ph3P=CHCO2Me
CO2Et
SePh
16

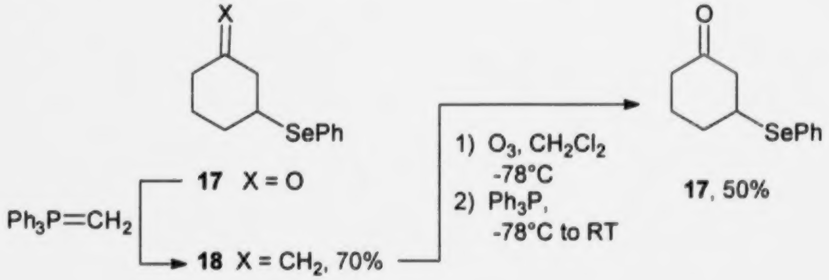
Scheme I-7

Thus, compounds **12**, **14**, and **16** were subjected under classical conditions to the action of ozone, and the resulting selenoxide-ozonide was exposed to the reducing agent triphenyl phosphine to furnish the benzeneseleno aldehydes **11**, **13**, and **15** in good yield, Scheme I-8. We have examined only triphenylphosphine as a reducing agent,[20] but we suspect that a number of other reducing agents, such as sodium sulfite, may also prove suitable. As can be seen from the examples shown in Scheme I-8 the double bond is oxidatively cleaved and the selenium unit retained.


1) O3, CH2Cl2
-78°C
2) Ph3P,
-78°C to RT
SePh
CHO
12
11, 93%
14
13, 84%
CO2Et
16
15, 83%

Scheme I-8

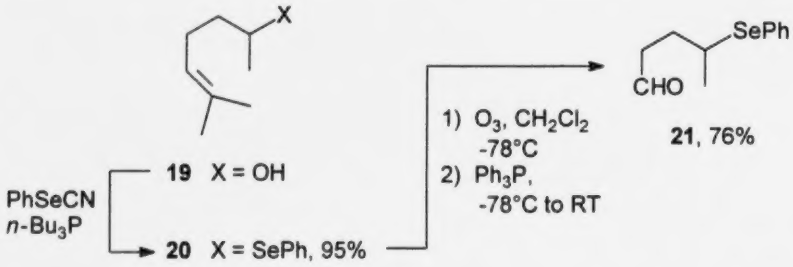
This is true even in the case of the example shown in Scheme I-9, wherein the intermediate selenoxide should be particularly labile because its collapse would generate an α,β-unsaturated carbonyl system.


X
O
SePh
Ph3P=CH2
17 X = O
18 X = CH2, 70%
1) O3, CH2Cl2
-78°C
2) Ph3P,
-78°C to RT
17, 50%

Scheme I-9

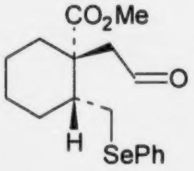
Even in this case, the yield is 50% and this modest yield is a reflection not of the undesired selenoxide fragmentation, but of the fact that selenide **17** is itself not particularly stable to silica gel chromatography. When we subjected a sample of selenide **17** to flash chromatography a 10% loss of material was observed.

Some of our compounds are primary selenides and it is known that primary selenoxides are much more stable than secondary selenoxides.[21] Consequently, we also examined the secondary selenide **20** and found that it underwent cleavage and subsequent reduction to aldehyde **21** in 76% yield, indicating that the methodology is not restricted to primary selenides, Scheme I-10.


X
19 X = OH
PhSeCN
n-Bu3P
20 X = SePh, 95%
1) O3, CH2Cl2
-78°C
2) Ph3P,
-78°C to RT
SePh
CHO
21, 76%

Scheme I-10

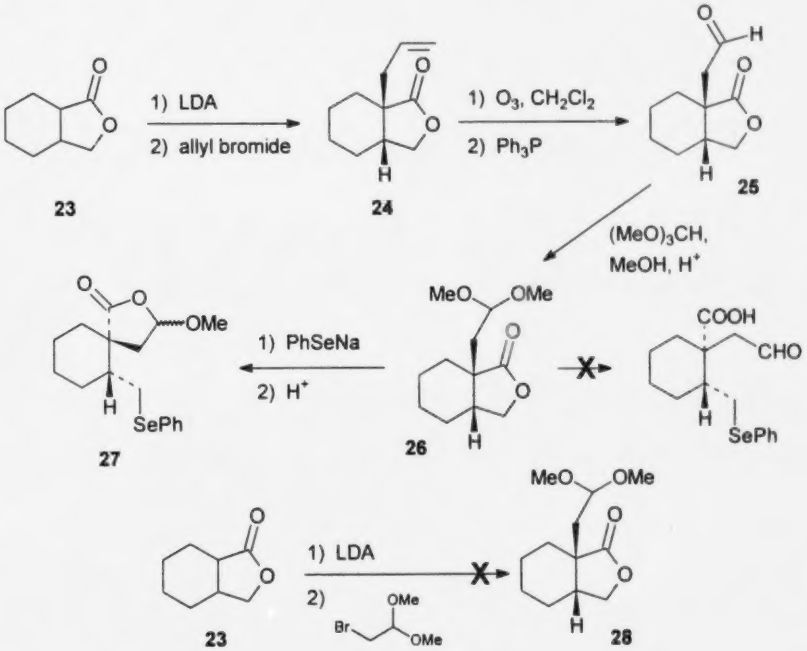
We conclude that the phenylseleno group can indeed be introduced before steps that involve ozonolytic cleavage of a double bond, and we believe that this information extends the synthetic utility of the phenylseleno group. One case in point is represented by our attempts to prepare the phenylseleno methyl aldehyde **22**, Fig. I-1.


CO2Me
O
H
SePh

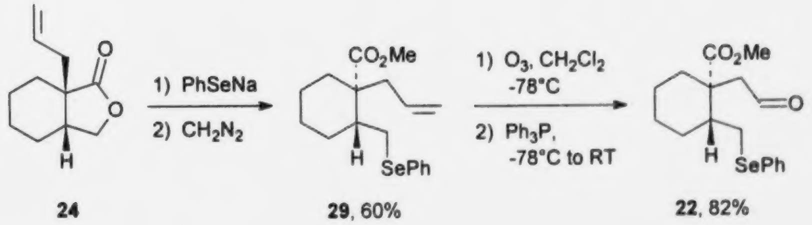
22

Figure I-1

We made a number of unsuccessful attempts to prepare this compound by routes that delayed introduction of the selenide function (Scheme I-11), but we found that the present route (Scheme I-12) is by far the best.


23
1) LDA
2) allyl bromide
24
1) O_3, CH_2Cl_2
2) Ph_3P
25
$(MeO)_3CH$,
MeOH, H^+
26
1) PhSeNa
2) H^+
27
SePh
COOH
CHO
SePh
23
1) LDA
2) Br OMe OMe
28
MeO OMe

Scheme I-11


24
1) PhSeNa
2) CH_2N_2
CO_2Me
SePh
29, 60%
1) O_3, CH_2Cl_2
-78°C
2) Ph_3P,
-78°C to RT
CO_2Me
SePh
22, 82%

Scheme I-12

Further work is underway in this laboratory to accumulate a broader range of examples of the ozonolysis of olefinic selenides with retention of the selenium unit.

EXPERIMENTAL

General. Argon was purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. Glassware was either flame-dried or dried in an oven for at least 3 h before use (120 °C) and cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars. Organic solutions were dried with $MgSO_4$, unless otherwise stated.

Solvents for chromatography were distilled before use. Petroleum ether refers to the fraction bp 35-60°C.

Products were isolated from solution by evaporation under water-pump vacuum at, or below, 30 °C, using a rotary evaporator.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60 F—254) were used. Spots were detected by examination under UV light and then by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes or cannulas. Dry tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone ketyl. Dry methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide, respectively. Dry benzene and toluene were distilled from sodium. Dry diisopropylamine, triethylamine, dichloromethane, pyridine, and *N,N*-dimethylformamide were distilled from calcium hydride, the last solvent being distilled under water-pump vacuum. Commercial (Aldrich) solutions of *n*-butyllithium and methyllithium (both in hexanes) were assumed to have the stated molarity.

Ozonolysis were peformed with a Helsbach ozonizer.

Infrared spectra were recorded on a Nicolet 7000 FT-IR model. Measurements were made as casts from the specified solvent and using potassium bromide plates.

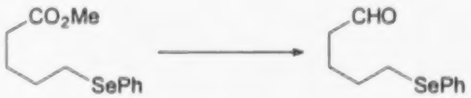
Proton nuclear magnetic resonance spectra were recorded with Bruker WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded with Bruker WP-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker AM-400 (at 100.6 MHz) spectrometers using deuterochloroform as an internal standard. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department.

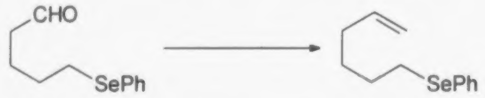
Compounds in Chapter 1 and 2 of this Thesis are racemic. The compounds synthesized in Chapter 3 of this work are optically pure.

5-(Phenylseleno)pentanal (11).



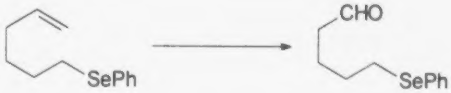
A solution of DIBAL (14.27 mL, 1.0M solution in CH_2Cl_2, 14.27 mmol) was added dropwise to a cold (-78°C) and stirred solution of **10** in CH_2Cl_2 (60 mL) via syringe over ca. 4 min. The resulting solution was stirred at -78°C for 30 min and then $Na_2SO_4 \cdot 10H_2O$ (4.0 g) was added in one portion, and the cold bath removed. Stirring was continued for 1 h, anhydrous Na_2SO_4 (10 g) was added, and the mixture was filtered through Celite (3 x 6 cm), using CH_2Cl_2 (200 mL) as eluent. The filtrate was evaporated, and flash chromatography of the residue over silica gel (3 x 21 cm), using 8% EtOAc-hexane, gave **11** (2.8201 g, 82%) as a pure [^1H NMR (400 MHz)] oil: FT-IR (CH_2Cl_2 cast) 3056, 2934, 2886, 2821, 2722, 1722, 1578, 1478, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.79 (m, including a t at δ 1.72, $J = 4$ Hz, 2 H), 2.36-2.48 (m, including a d at δ 2.41, $J = 1.5$ Hz, 2 H), 2.85-2.98 (m, including a t at δ 2.90, $J = 7$ Hz, 2 H), 7.20-7.30 (m, 3 H), 7.41-7.52 (m, 2 H), 9.71 (t, $J = 1.5$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.90 (t'), 27.12 (t'), 29.32 (t'), 42.99 (t'), 126.62 (d'), 128.67 (d'), 130.02 (s'), 132.34 (d'), 201.76 (d'); exact mass, *m/z* calcd for $C_{11}H_{14}OSe$ 242.1210, found 242.1211. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.72; H, 5.91.

6-(Phenylseleno)-1-hexene (12).



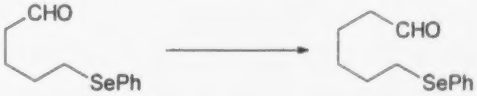
n-BuLi (1.33 mL, 1.6M, 2.13 mmol) was added dropwise over ca. 30 sec to a stirred and cooled (-20°C) suspension of methyl triphenylphosphonium bromide (777.9 mg, 2.13 mmol) in THF (20 mL). The resulting yellow solution was stirred for 20 min at 0°C, cooled to -78°C, and then added via cannula (using THF 5 mL as rinse) to a stirred and cooled (-78°C) solution of aldehyde **11** (468.0 mg, 1.94 mmol) in THF (30 mL) over ca 30 sec. The cold bath was removed and the solution was stirred for 12 h, quenched with water (5 mL), followed by 10% aqueous HCl (20 mL). The aqueous solution was extracted with CH_2Cl_2 (4 x 20 mL), and the combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 15% CH_2Cl_2-hexane, gave **12** (328.7 mg, 71%) as a pure [^{1}H NMR (400 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 3072, 3059, 2674, 2929, 2854, 1640, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (pentet, *J* = 7.5 Hz, 2 H), 1.73 (pentet, *J* = 5 Hz, 2 H), 2.90 (t, *J* = 7.5 Hz, 2 H), 4.92-5.04 (m, 2 H), 5.71-5.83 (m, 1 H), 7.18-7.29 (m, 3 H), 7.42-7.50 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 27.62 (t'), 28.93 (t'), 29.52 (t'), 33.09 (t'), 114.63 (t'), 126.54 (d'), 128.90 (d'), 130.57 (s'), 132.34 (d'), 138.33 (d'); exact mass, *m/z* calcd for $C_{12}H_{16}Se$ 240.0404, found 240.0417. Anal. Calcd for $C_{12}H_{16}Se$: C, 60.25; H, 6.74. Found: C, 60.55; H, 6.79.

5-(Phenylseleno)pentanal (11).



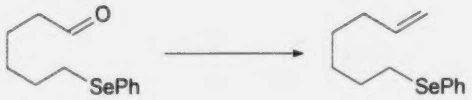
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cooled (-78°C) solution of selenide **12** (143.7 mg, 0.661 mmol) in CH_2Cl_2 (35 mL) until a permanent purple color was generated (ca. 5 min). Triphenylphosphine (500 mg, 1.90 mmol) was then added in 1 portion and, with the cold bath in place, the solution was stirred for 3-4 hr, by which point the solution had attained room temperature. The solution was concentrated, and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave **11** (134.4 mg, 93%) as a pure [^{1}H NMR, (400MHz)], oil, spectroscopically identical (^{1}H NMR, ^{13}C APT, FT-IR) to an authentic sample made by DIBAL reduction of the corresponding ester **10**.

6-(Phenylseleno)hexanal (13).



n-BuLi (9.91 mL, 1.6M, 15.85 mmol) was added to a stirred and cooled (-78° C) solution of (methoxymethyl)triphenylphosphonium chloride (5.44 g, 15.85 mmol) in THF (30 mL) over 1 min. The resulting orange solution was stirred for 30 min at 20°C and then added via cannula (using THF 5mL as rinse) to a stirred and cooled (-78°C) solution of aldehyde **11** (1.9119 g, 7.93 mmol) in THF (50 mL). The cold bath was removed and the resulting solution was stirred for 36 h, poured into water (100 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The organic extract was dried and evaporated. The resulting oil was dissolved in *p*-dioxane (50 mL) and water (7 mL) and *p*-toluenesulfonic acid (200 mg) was added. The solution was stirred for 12 h at room temperature and then refluxed 24 h and cooled. The resulting mixture was extracted with ether (3 x 50 mL) and the organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using EtOAc-hexane mixtures (3 to 6% EtOAc), gave **13** (1.2519 g, 62%) as a pure [^{1}H NMR, (400MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 2932, 2857, 2821, 2720, 1723, 1578, 1478 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38-1.49 (m, 2 H), 1.61 (pentet, *J* = 7.5 Hz, 2 H), 2.38 (t, *J* = 7.5 Hz, 2 H), 2.91 (t, *J* = 7.5 Hz, 2 H), 7.16-7.30 (m, 3 H), 7.42-7.53 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.13 (t'), 27.13 (t'), 28.84 (t'), 29.48 (t'), 43.27 (t'), 126.35 (d'), 128.69 (d'), 130.15 (s'), 132.06 (d'), 201.84(d'); exact mass, *m/z* calcd for $C_{12}H_{16}OSe$ 256.0366, found 256.0369. Anal. Calcd for $C_{12}H_{16}OSe$: C, 56.47; H, 6.32. Found: C, 56.64; H, 6.52.

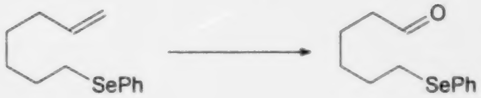
7-(Phenylseleno)-1-heptene (14).



n-BuLi (1.06 mL, 1.6M, 1.69 mmol) was added dropwise over ca. 1 min to a stirred and cooled (-20°C) suspension of methyl triphenylphosphonium bromide (617.8 mg, 1.69 mmol) in THF (60 mL). The resulting yellow solution was stirred for 20 min at 0°C, cooled to -78°C, and then added via cannula over ca. 30 sec (using THF 3 mL as rinse) to a stirred and cooled (-78°C) solution of aldehyde **13** (393.2 mg, 1.54 mmol) in THF (30 mL). The cold bath was removed and the solution was stirred for 8 h, quenched with water (5 mL), followed by 10% aqueous HCl (20 mL). The aqueous solution was extracted with CH_2Cl_2 (4 x 25 mL), and the combined organic extracts washed with brine (1 x 15 mL), dried, and evaporated. Flash chromtaography of the residue over silica gel (3 x 15 cm), using 15% CH_2Cl_2-hexane,

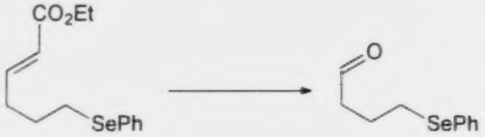
gave **14** (281.8 mg, 72%) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 3073, 3060, 2974, 2928, 1640, 1579, 1477 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.47 (m, 2 H), 1.65-1.76 (m, 2 H), 1.98-2.06 (m, 2 H), 2.89 (t, *J* = 7.5 Hz, 2 H), 4.89-5.02 (m, 2 H), 5.72-5.85 (m, 1 H), 7.17-7.29 (m, 3 H), 7.42-7.52 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 27.79 (t'), 28.30 (t'), 29.25 (t'), 29.96 (t'), 33.57 (t'), 114.41 (t'), 126.58 (d'), 128.94 (d'), 130.63 (d'), 132.38 (d'), 138.74 (d'); exact mass, *m/z* calcd for $C_{13}H_{18}OSe$ 254.0574, found 254.0568. Anal. Calcd for $C_{13}H_{18}OSe$: C, 61.66; H, 7.16. Found: C, 61.78; H, 7.27.

6-(Phenylseleno)-1-hexanal (13).



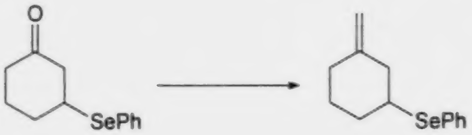
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cooled (-78°C) solution of selenide **14** (174.9 mg, 0.691 mmol) in CH_2Cl_2 (30 mL) until a permanent the purple color was generated (ca. 5 min). Triphenylphosphine (1.2 g, 4.56 mmol) was then added in one portion, and with the cold bath in place, the solution was stirred for 3-4 hr at which point it had attained room temperature. The solution was concentrated, and flash chromatography of the residue over silica gel (2.5 x 19 cm), using 5% EtOAc-hexane, gave **13** (147.4 mg, 84%) as a pure [2-D TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)] oil which was spectroscopically identical (^{1}H NMR, ^{13}C APT, FT-IR) to an authentic sample of **13** made by Wittig reaction from **11**.

4-(Phenylseleno)-1-butanal (15).



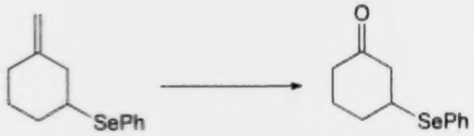
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cooled (-78°C) solution of olefin **16**[22] (256.3 mg, 0.862 mmol) in CH_2Cl_2 (30 mL) until a permanent purple color was generated (ca. 7 min). Triphenylphosphine (680 mg, 2.59 mmol) was then added in one portion, and with the cold bath in place, the solution was stirred for 3-4 h at which point it had attained room temperature. The solution was concentrated, and flash chromatography of the residue over silica gel (2.5 x 18 cm), using EtOAc-hexane mixtures (5 to 8% EtOAc) gave **15** (163.2 mg, 83%) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (neat film) 3070, 3056, 2938, 2823, 1723, 1578, 1478, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92-2.02 (m, including a pentet at δ 1.98, 2 H), 2.57 (dt, *J* = 7.5, 1.5 Hz, 2 H), 2.91 (t, *J* = 8.5 Hz, 2 H), 7.18-7.28 (m, 3 H), 7.41-7.50 (m, 2 H), 9.72 (t, *J* = 1.5 Hz, 1 H); exact mass, *m/z* calcd for $C_{10}H_{12}OSe$ 228.0053, found 228.0044.

3-(Phenylseleno)-1-methylenecyclohexane (18)



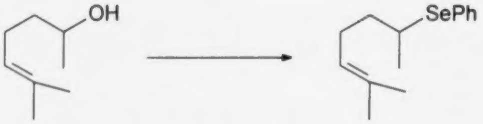
n-BuLi (4.30 mL, 1.6M, 6.88 mmol) was added dropwise over ca. 30 sec to a stirred and cooled (-78°C) suspension of methyl triphenylphosphonium bromide (2.4674 g, 6.89 mmol) in THF (15 mL). The resulting yellow solution was stirred for 20 min at 0°C, cooled to -78°C, and then added via cannula over ca. (using THF 5 mL as rinse) to a stirred and cooled (-78°C) solution of phenylseleno ketone **17**[23] (1.5853 g, 6.26 mmol) in THF (20 mL). The cold bath was removed and the solution was stirred for 10 h, quenched with water (7 mL), followed by 10% aqueous HCl (30 mL). The aqueous solution was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried, and evaporated. Flash chromtaography of the residue over silica gel (3 x 21 cm), using 15% CH_2Cl_2-hexane, gave **18** (1.1083 mg, 70%) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2979, 2933, 2882, 2834, 1650, 1578, 1476, 1436, 1336, 1226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30-1.45 (m, 1 H), 1.52-1.65 (m, 1 H), 1.75-1.88 (m, 1 H), 1.93-2.09 (m, 2 H), 2.14-2.27 (m, 2 H), 2.60 (dd, *J* = 13, 4 Hz, 1 H), 3.19-3.31 (m, 1 H), 4.62 (d, *J* = 14 Hz, 2 H), 7.18-7.28 (m, 2 H), 7.46-7.55 (m, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 27.47 (t'), 33.34 (t'), 34.28 (t'), 42.52 (t'), 43.27 (d'), 108.69 (t'), 127.38 (d'), 128.91 (d'), 128.99 (s'), 134.82 (d'); exact mass, *m/z* calcd for $C_{13}H_{16}OSe$ 252.0417, found 252.0416. Anal. Calcd for $C_{13}H_{16}OSe$: C, 62.15; H, 6.42. Found: C, 62.27; H, 6.58.

3-(Phenylseleno)-1-cyclohexanone (17)



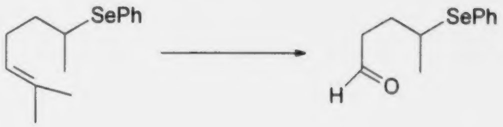
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cooled (-78°C) solution of olefin **18** (279.3 mg, 1.11 mmol) in CH_2Cl_2 (25 mL) until a permanent purple color was generated (ca. 6 min). Triphenylphosphine (1.18 g, 4.5 mmol) was then added in one portion and, with the cold bath in place, the solution was stirred for 3-4 h, at which point it had attained room temperature. The solution was concentrated, and flash chromatography of the residue over silica gel (2.5 x 19 cm), using 5% EtOAc-hexane, gave **17** (141.4 mg, 50%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)] oil which was spectroscopically identical to an authentic sample of **17**.

2-Methyl-6-(phenylseleno)-2-heptene (20).



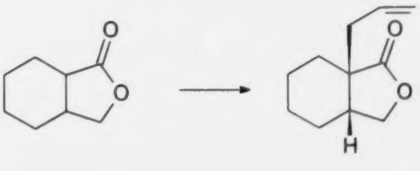
A literature procedure[24] for conversion of alcohols to phenyl selenides was followed with minor modifications. *n*-Bu$_3$P (1.46 mL, 5.86 mmol) and PhSeCN (1.07 mg, 5.86 mmol) were sequentially added to a stirred and cooled (0°C) solution of alcohol **19**[25] (375.3 mg, 2.93 mmol) in THF (7 mL). The resulting solution was stirred for 4 h and then concentrated. Flash chromatography of the residue over silica gel (2.5 x 19 cm), using 3% CH$_2$Cl$_2$-hexane, gave **20** (741.8 mg, 95%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], yellow oil: FT-IR (CH$_2$Cl$_2$ cast) 3071, 2966, 2917, 2858, 1579, 1476, 1376, 1073 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.40 (d, $J = 12$ Hz, 3 H), 1.50-1.80 (m, including s at δ 1.60 and δ 1.69, 8 H), 2.05-2.20 (m, 1 H), 3.20-3.39 (m, 1 H), 5.00-5.10 (m, 1 H), 7.20-7.31 (m, 2 H), 7.47-7.61 (m, 3 H); ^{13}C NMR APT (CDCl$_3$, 100.6 MHz) δ 17.74 (q'), 22.18 (q'), 25.71 (q'), 26.38 (t'), 37.58 (t'), 39.26 (d'), 123.62 (d'), 127.25 (d'), 128.83 (d'), 129.42 (s'), 132.15 (s'), 134.89 (d'); exact mass, *m/z* calcd for C$_{14}$H$_{20}$OSe 268.0730, found 268.0726. Anal. Calcd for C$_{14}$H$_{20}$OSe: C, 62.91; H, 7.54. Found: C, 62.92; H, 7.74.

4-(Phenylseleno)-1-pentanal (21)



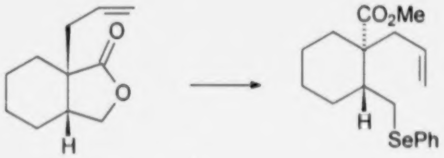
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cooled (-78°C) solution of olefin **20** (182.8 mg, 0.684 mmol) in CH_2Cl_2 (30 mL) until a permanent purple color was generated (ca. 6 min). Triphenylphosphine (900 mg, 3.42 mmol) was then added in one portion, and with the cold bath in place, the solution was stirred for 3-4 hr at which point it had attained room temperature. The solution was concentrated, and flash chromatography of the residue over silica gel (2.5 x 23 cm), using 5% EtOAc-hexane gave **21** (124.8 mg, 76%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2954, 2919, 2862, 2822, 1723, 1578, 1477, 1389, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, J = 7 Hz, 3 H), 1.85-1.99 (m, 2 H), 2.63 (t, J = 7 Hz, 2 H), 3.21-3.31 (m, 1 H), 7.20-7.31 (m, 3 H), 7.49-7.58 (m, 2 H), 9.75 (m, J = 2 Hz, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.16 (q'), 29.50 (t'), 38.86 (q'), 42.08 (t'), 127.63 (d'), 128.52 (s'), 128.96 (d'), 135.02 (d'), 201.50 (d'); exact mass, *m/z* calcd for $C_{11}H_{14}OSe$ 242.0210, found 242.0208. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.74; H, 5.96.

Cis-7a-(2-Propenyl)hexahydro-1(3*H*)-isobenzofuranone (24).



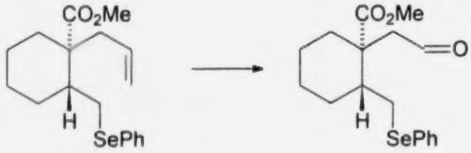
Lithium diisopropylamide (LDA) was prepared by rapid additon (ca. 60 sec) of *n*-BuLi (18.52 mL, 1.6M in hexane, 29.63 mmol) to a magnetically stirred and cooled (0°C) solution of *i*-Pr_2NH (4.13 mL, 29.63 mmol) in THF (35 mL). The solution was then cooled to -78°C, and after an additional 15 min, a solution of the lactone **23** (2.7687, 19.76 mmol) in THF (15 mL plus 5 mL as rinse) was added by cannula over ca. 1 min. The resulting solution was stirred for 30 min, and then *n*-BuLi (6 mL, 1.6M, 9.60 mmol) was added and the solution was stirred for 10 min at -78°C at which point allyl bromide (2.80 mL, 32 mmol) was added neat in one portion. The cold bath was removed and stirring was continued for 8 h. Cold saturated aqueous ammonium chloride (10 mL) was added and the solution was extracted with ether (3 x 35 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 5% EtOAc-hexane, gave **24** (2.8408 g, 80%) as a pure [^{1}H NMR (400 MHz)], pale yellow oil: FT-IR ($CDCl_3$ cast) 2933, 2858, 1768, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.57 (br m, 6 H), 1.63-1.82 (m, 2 H), 2.25-2.40 (m, 3 H), 3.95 (dd, *J* = 9.0, 5.5 Hz, 1 H), 4.25 (dd, *J* = 9, 6 Hz, 1 H), 5.02-5.15 (m, 2 H), 5.66-5.80 (m, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.68 (t'), 21.92 t'), 25.07 (t'), 29.29 (t'), 37.71 (d'), 38.92 (t'), 44.96 (s'), 69.21 (t'), 118.78 (t'), 132.93 (d'), 180.96 (s'); exact mass, *m/z* calcd for $C_{11}H_{16}O_2$ 180.1156, found 180.1149. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.26; H, 8.98.

Methyl *cis*-1-(2-propenyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (29).



A literature procedure for cleavage of lactones, using phenyl selenide anion,[6] was followed with slight modifications: THF (5 mL) was added to a stirred mixture of PhSeSePh (1.0488 g, 3.36 mmol) and NaH (242.0 mg, 60% dispersion in oil, 6.05 mmol) and the resulting slurry was refluxed for 45 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature and dry HMPA (2.0 mL) was added. The precipitate dissolved, and a solution of lactone **24** (806.8 mg, 4.48 mmol) in THF (3 mL plus 2 mL as rinse) was added via cannula, and the mixture was refluxed for 36 h. The mixture was cooled to room temperature, quenched with methanol (8 mL), acidified (litmus red) by addition of cold hydrochloric acid (0.5M, 10 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **29**. Evaporation of the ether and flash chromatography of the residue over silica gel (3 x 20 cm), using EtOAc-hexane mixtures (2 to 20% EtOAc), gave selenide **29** (947.5 mg, 60%) as a pure [^{1}H NMR, (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2934, 1772, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.43 (m, 2 H), 1.47-1.93 (m, 4H), 1.70-1.80 (m, 1 H), 1.82-1.97 (m, 2 H), 2.49 (d, J = 8.5 Hz, 2 H), 2.97 (t, J = 12 Hz, 1 H), 3.14 (dd, J = 12 Hz, 2.5 Hz, 1 H), 3.65 (s, 3 H), 4.99-5.05 (m, 2 H), 5.55-5.63 (m, 1 H), 7.20-7.30 (m, 3 H), 7.49-7.59 (m, 2 H); ^{13}C NMR APT δ 22.15 (t'), 23.20 (s'), 26.35 (t'), 30.11 (t'), 40.90 (t'), 43.53 (d'), 50.61 (t'), 51.24 (q'), 118.25 (t'), 126.78 (d'), 128.92 (d'), 130.68 (s'), 132.88 (d'), 133.20 (d'), 175.91 (s'); exact mass, *m/z* calcd for $C_{18}H_{24}SeO_2$ 352.0929. found 352.0949. Anal. Calcd for $C_{18}H_{24}SeO_2$: C, 61.53; H, 6.89; O, 9.11. Found: C, 61.65; H, 6.88; O, 8.93.

Methyl *cis*-1-(2-oxoethyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (22).



Ozone (pre-cooled to -78 °C) was bubbled into a stirred and cooled (-78°C) solution of olefin **29** (167.4 mg, 0.476 mmol) in CH_2Cl_2 (30 mL) until a permanent purple color was generated (ca. 6 min). The solution was purged for 5 min with argon, and then triphenylphosphine (500 mg, 1.91 mmol) was added in one portion. The resulting solution was allowed to warm to room temperature with stirring with the cold bath in place (~ 4 hr). The cold bath was left in place and stirring was continued for ca. 4 h. The solution was concentrated, and flash chromatography of the residue over silica gel (2 x 27 cm), using EtOAc-hexane mixtures (2 to 18% EtOAc), gave aldehyde **22** (138.7 mg, 82%) as a pure [^{1}H NMR, (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2940, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.52 (m, 3 H), 1.53-1.73 (m, 4 H), 1.82-1.93 (m, 1 H), 2.04-2.12 (m, 1 H), 2.55 (dd, J = 13, 5.5 Hz, 1 H), 2.79-2.92 (m, 2 H), 3.00-3.06 (m, 1 H), 3.67 (s, 3 H), 7.20-7.30 (m, 3 H), 7.42-7.51 (m, 2 H), 9.62 (t, J = 1 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.90 (t'), 22.97 (t'), 26.29 (t'), 29.58 (t'), 31.35 (s'), 44.21 (d'), 47.72 (t'), 50.56 (t'), 51.68 (q'), 127.04 (d'), 129.03 (d'), 130.23 (s'), 132.90 (d'), 174.79 (s'), 200.11 (d'); exact mass, *m/z* calcd for $C_{17}H_{22}O_3Se$ 354.0730, found 354.0742. Anal. Calcd for $C_{17}H_{22}O_3$: C, 57.79; H, 6.28. Found: C, 58.02; H, 6.26.

REFERENCES

1. *Organoselenium Chemistry*, Liotta, D. Ed. Wiley Interscience, New York, 1987.
2. Clive, D.L.J. *Tetrahedron*, **1978**, *34*, 1049.
3. Clark, R.D.; Heathcock, C. *J. Org, Chem.* **1976**, *41*, 1485.
4. Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Org. Chem.* **1974**, *39*, 2133.
5. Denis, J.N.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1970**, 453.
6. Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.
7. Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28.
8. Sharpless, K.B.; Lauer, R.F *J. Am. Chem. Soc.* **1973**, 95, 2697.
9. Grieco, P.A.; Masaki, Y.; Boyler, D. *J. Am. Chem. Soc.* **1975**, *97*, 1597.
10. Lysenko, Z.; Ricciardi, F.; Semple, J.E.; Wang, P.C.; Joullie, M.M. *Tetrahedron Lett.* **1978**, 2679.
11. Grieco, P.A.; Miyashita, M. *J. Org, Chem.* **1974**, *39*, 120.
12. Jaurand, G.; Beau, J.-M.; Sinaÿ,P. *J. Chem. Soc., Chem. Commun.* **1981**, 572.
13. Gaskin, P.; MacMillan, J.; Makinson, I.K.; Willis, C.L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1359.
14. Clive, D.L.J.; Angoh, A.G.; Suri, S.C.; Nagaraja Rao, S.; Russell, C.G. *J. Chem. Soc., Chem. Commun.* **1982**, 828.
15. Baudat, R.; Petrzilka, M. *Helv. Chim. Acta.* **1979**, *62*, 1406.
16. Barton, D.H.R.; Lester, D.J. Motherwell, W.B. and Papoula, M.T.B. *J. Chem. Soc., Chem. Commun.* **1980**, 246.
17. Posner, G.H.; Chapdelaine, M.J. *Tetrahedron Lett.* **1977**, 3277..
18. Shimizu, M.; Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1981**, *22*, 2183.

19. Ayrey, G.; Barnard, D.; Woodbridge, D.T. *J. Chem. Soc.* **1962**, 2089.

20. Tamagaki, S.; Hatanaka, I.; Tamura, K. *Chemistry Lett.* **1976**, 81.

21. Sharpless, K.B.; Young, M.W. *J. Org, Chem.* **1975**, *40*, 947.

22. The author thanks Craig Railton for a sample of **16**.

23. Prepared by 1,4-addition of phenylselenol to cyclohexenone in benzene, catalyzed by triethylamine.

24. Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

25. Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org, Chem.* **1979**, *44*, 3888.

Chapter 2

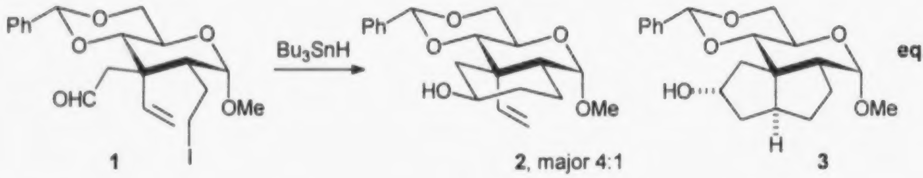
trans Ring Fused Bicyclic Structures by 6-*exo*-Trigonal Radical Closure: Use of the Triethylborane-Stannane-Air System for Intramolecular Addition to Aldehydes

INTRODUCTION

The area of synthetic free radical chemistry has been reviewed on a number of occasions.[1] The majority of radical additions in the literature are those involving addition to carbon-carbon multiple bonds, but recently, radical additions to carbon-heteroatom multiple bonds have begun to gain acceptance as a useful synthetic tool. The present review section will discuss some of the recent developments in this area. A general outline of the principles of additions to carbonyl groups will be followed by a summary of the synthetic applications of this methodology.

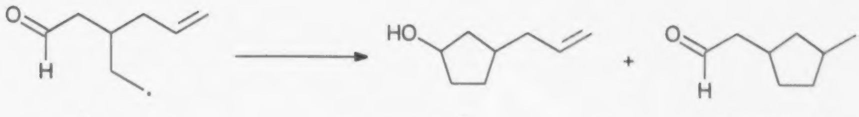
Radical Addition to Aldehydes

Fraser-Reid and Tsang[2] were the first to observe that 6-*exo* free radical cyclization onto aldehydes was a useful synthetic procedure. Reaction of **1** with tributyltin hydride gave a mixture of two compounds **3** and **2** in a 1:4 ratio and in 91% combined yield.



eq. II-1

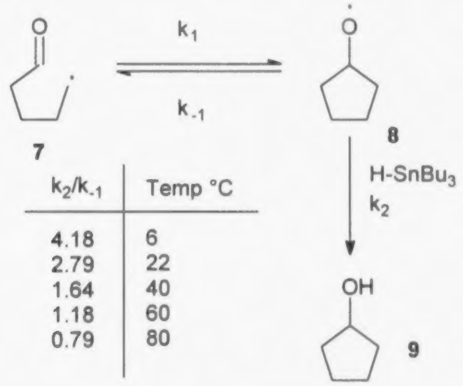
Fraser-Reid and co-workers[3] have studied the competitive reaction between 5-*exo* cyclization onto a carbonyl group and 5-*exo* cyclization onto an olefin. In this experiment it was found that olefin closure product dominated by a ratio of 3:1 (eq. II-2). This is an upper limit, since the reversibility of the cyclization was not taken into account.



4 **5** **6**, major 3:1

eq. II-2

These results (and others by the same group, *vide infra*) have prompted mechanistic work in this area. Beckwith and co-workers[4] have shown that the rate constant of 5-*exo* closure for radical **7** to **8** is $k_1 = 8.7 \times 10^6\ s^{-1}$ at 80 °C, while the rate constant for the reverse reaction (ring opening or fragmentation) has been found to be quite large and estimated at $k_{-1} = 4.7 \times 10^8\ s^{-1}$ at 80 °C.

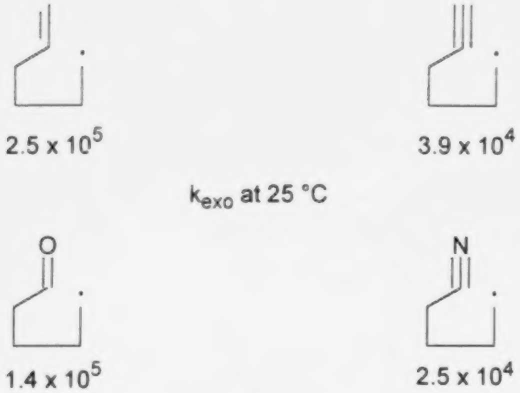


7 **8** **9**

k_2/k_{-1}	Temp °C
4.18	6
2.79	22
1.64	40
1.18	60
0.79	80

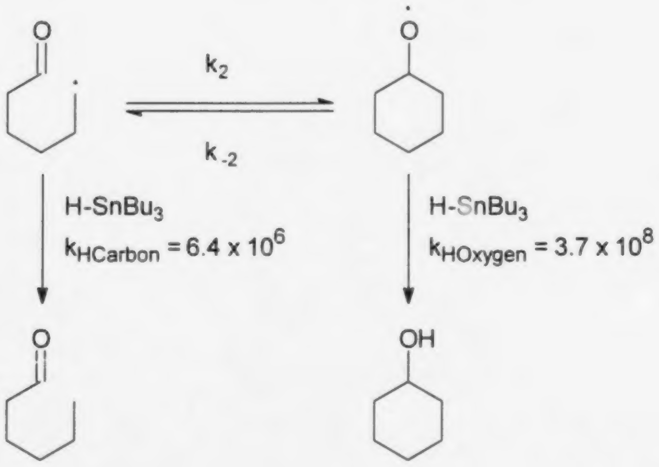
Scheme II-1

The results in Scheme II-1 would seem to indicate that at lower temperature fragmentation of the alkoxy radical is less pronounced, but the bimolecular reaction of recudtion of the alkoxy radical is also effected by variations in temperature and it is not clear how this will effect the outcome of the process. The rate constants for various acceptors are listed in Scheme II-2 and they show that the rate constants for radical cyclizations onto olefins, aldehydes, and alkynes are within the useful range, whereas the rate of cyclization for 5-*exo* closure onto a nitrile is rather low and this may cause premature reduction of the initial radical before it can cyclize.


2.5 x 10^5
3.9 x 10^4
k_exo at 25 °C
O
N
1.4 x 10^5
2.5 x 10^4

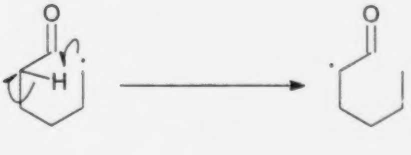
Scheme II-2

The six-membered case is slightly more complicated.[5] The rate constant for 6-*exo* closure has been measured at 1.0 x 10^6 s^{-1} at 80 °C, while the rate constant for ring opening is only slightly faster, with a value of 1.1 x 10^7 s^{-1}, also at 80 °C.


O
k2
k-2
O
H-SnBu3
kHCarbon = 6.4 x 10^6
H-SnBu3
kHOxygen = 3.7 x 10^8
O
OH

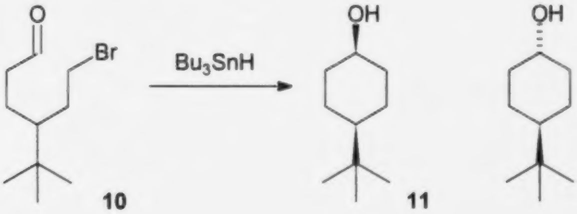
Scheme II-3

Another factor to consider in the 6-*exo* aldehyde cyclizations is the problem of hydrogen abstraction via a six-membered ring transition state. Beckwith has shown that at low stannane concentration this reaction is competitive with cyclization (eq. II-3).



eq. II-3

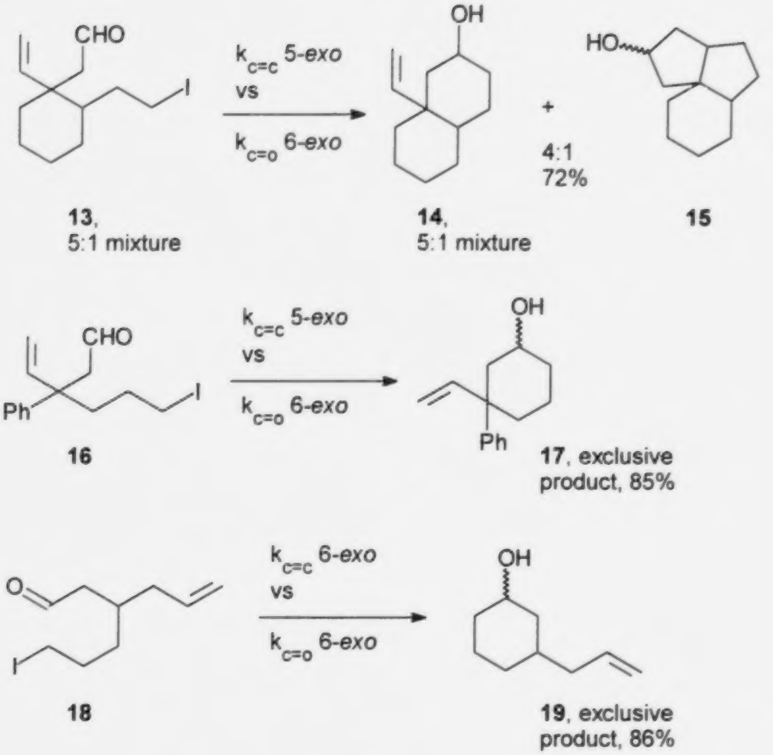
The stereochemistry of cyclization has also been studied[6] for the 6-*exo* cyclization with aldehyde **10** (eq. II-4) and it has been established that at high stannane concentration the *trans/cis* ratio is 1.2, while at low concentration the ratio increases to 3.2. This is explained by assuming that at high stannane concentration the alkoxy radical is quenched immediately while at low stannane concentration equilibration occurs via the open chain form and the thermodynamically favored product **12** is formed preferentially. This arguement does not take Curtin-Hammet kinetics into account and also the ring opening reaction is not a favoured process.



10 **11** **12**

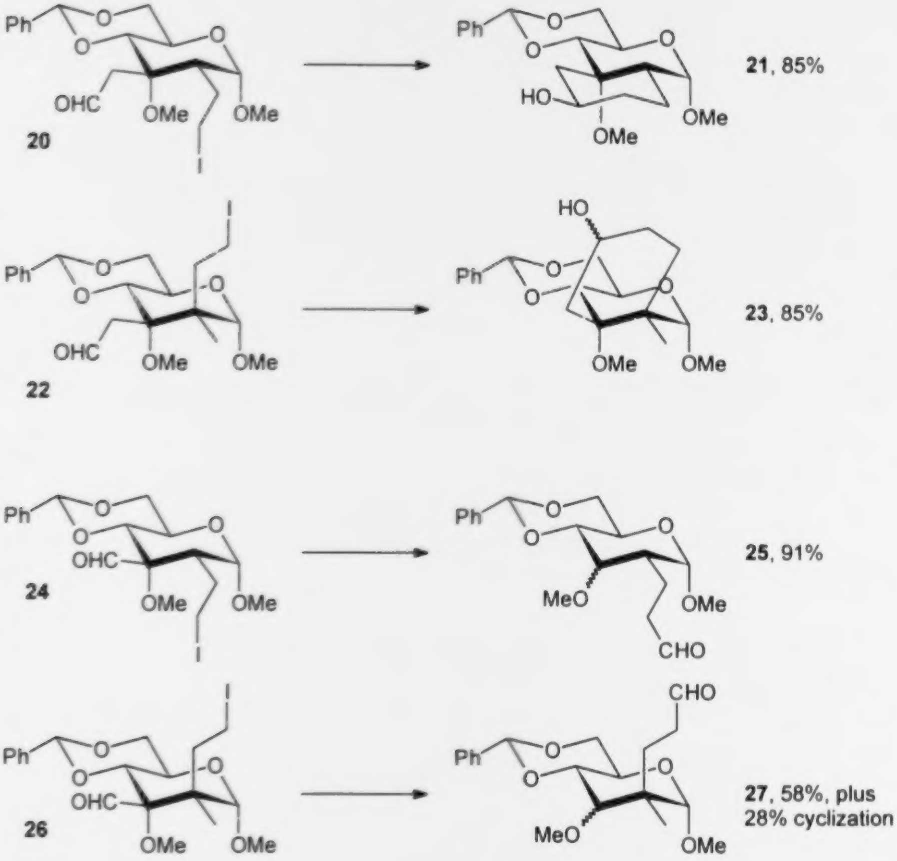
eq. II-4

Further work by Fraser-Reid and Walton[7] has indeed shown that aldehydes are synthetically useful radical acceptors. In competitive studies between *exo* cyclization onto olefins and aldehydes they have observed that the 6-*exo* aldehyde cyclization is favored over both 5-*exo* and 6-*exo* olefin cyclizations (Scheme II-4).


CHO
k_{C=C} 5-exo
vs
k_{C=O} 6-exo
OH
HO
+
4:1
72%
13,
5:1 mixture
14,
5:1 mixture
15
CHO
Ph
I
k_{C=C} 5-exo
vs
k_{C=O} 6-exo
OH
Ph
16
17, exclusive
product, 85%
O
I
k_{C=C} 6-exo
vs
k_{C=O} 6-exo
OH
18
19, exclusive
product, 86%

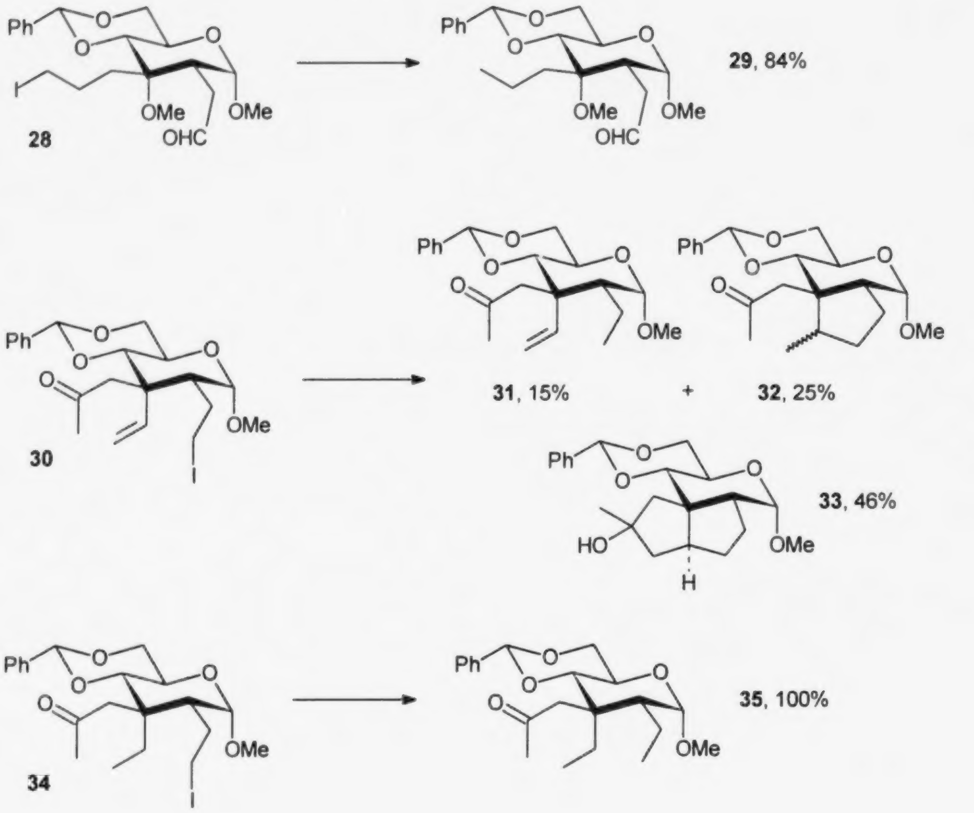
Scheme II-4

Other examples have also been studied by the Duke University group[8] to better understand the scope of this reaction. The first two entries in Scheme II-5 show that 6-*exo* cyclization onto the aldehyde carbon is an efficient process even though fragmentation would give a stable α-oxygen radical. The corresponding 5-*exo* cyclizations gave did not always proceed as efficiently, since fragmentation was found to be the major pathway in the case of **24**.



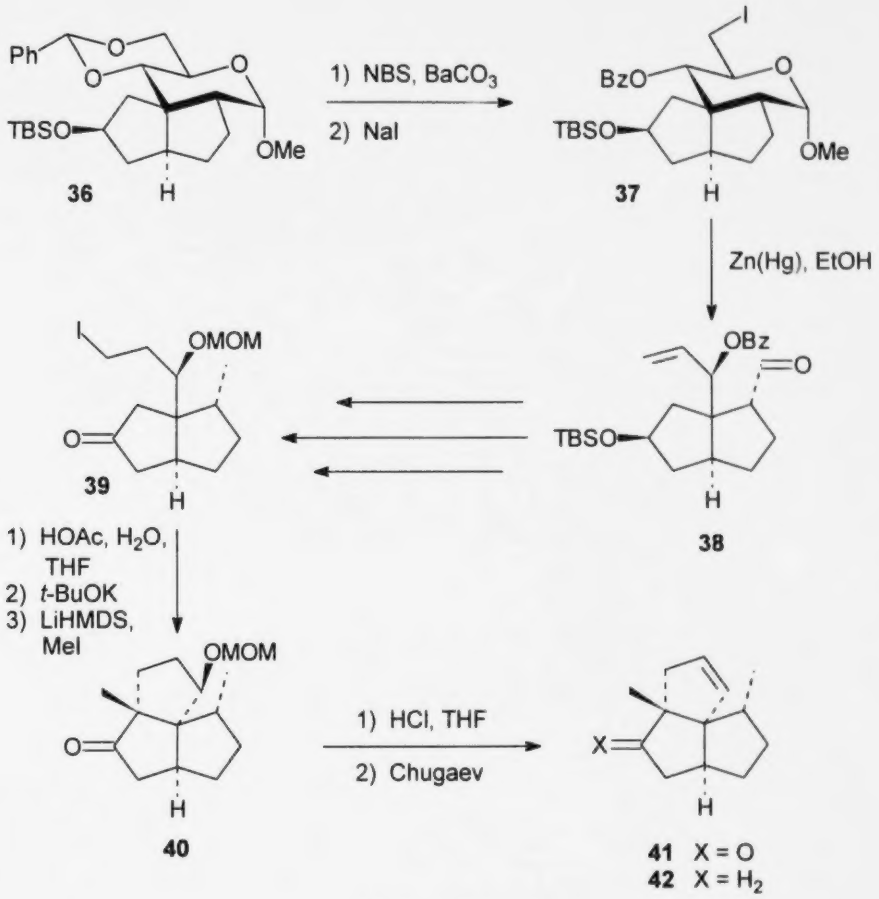
Scheme II-5

The corresponding 7-*exo* cyclization and cyclization onto a ketone (Scheme II-6) were also examined. Attempted 7-*exo* trigonal cyclization gave only the product of reduction. Tandem cyclization of **30** did provide an interesting set of results. Three compounds were isolated from this reaction. The reduction product **31** was formed in 15% while the isomeric products **32**, derived from cyclization onto the olefin, were formed in 25%. The tandem cyclization product **33** was formed in 46% yield! This is a very interesting result since the 5-*exo* cyclization onto the ketone was a favoured process, but other products (**32** and **33**) were also isolated from the reaction mixture.


Ph
O
O
O
I
OMe
OMe
OHC
28
29, 84%
30
31, 15%
+
32, 25%
33, 46%
HO
H
34
35, 100%

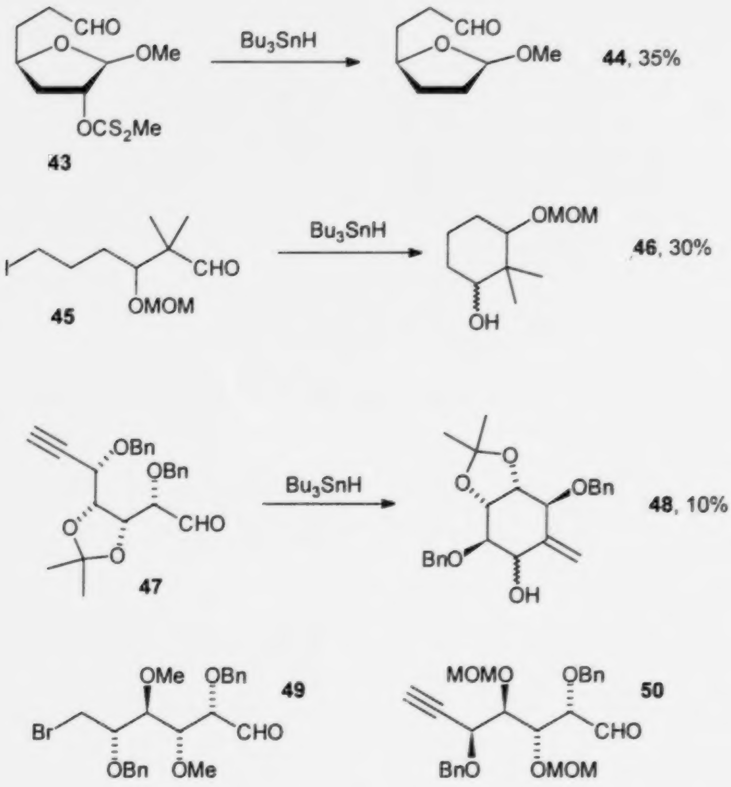
Scheme II-6

A synthetic application of this methodology[9] to the synthesis of silphenene (**42**) is shown in Scheme II-7. The benzylidene group of **36** was opened to afford **37** and fragmentation then provided **38**. Functional group manipulations gave **39** and alkylation then gave a mixture of isomers that was deprotonated and methylated to **40**. Finally, deprotection and Chugaev elimination furnished **41**, a compound that has been previously transformed into **42**.


Ph
TBSO
OMe
H
36
1) NBS, BaCO$_3$
2) NaI
I
BzO
TBSO
OMe
H
37
Zn(Hg), EtOH
OBz
TBSO
H
38
OMOM
I
39
H
1) HOAc, H$_2$O, THF
2) t-BuOK
3) LiHMDS, MeI
OMOM
40
H
1) HCl, THF
2) Chugaev
X
H
41 X = O
42 X = H$_2$

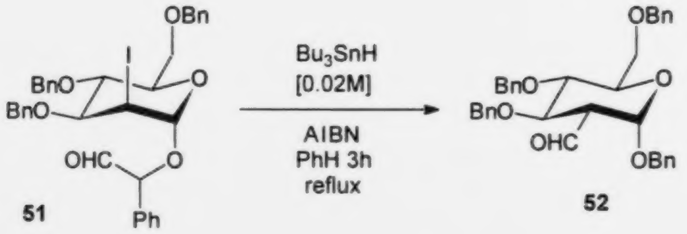
Scheme II-7

Not all the attempted cyclizations onto aldehydes have been successful.[10] The three entries in Scheme II-8 illustrate this point. Presumably, this is due to the effect of an α-oxygen functionality (that may cause fragmentation of the formed alkoxy radical) as well as encumberance of the aldehydo group. Starting materials that gave poor results are also depicted in Scheme II-9. The authors caution workers to choose substrates for radical-aldehyde chemistry with care since differing structural features seem to drastically alter the outcome of these reactions.


CHO
OMe
OCS$_2$Me
43
Bu$_3$SnH
CHO
OMe
44, 35%
I
CHO
OMOM
45
Bu$_3$SnH
OMOM
OH
46, 30%
OBn
OBn
CHO
47
Bu$_3$SnH
OBn
BnO
OH
48, 10%
OMe
OBn
49
Br
CHO
OBn
OMe
MOMO
OBn
50
CHO
BnO
OMOM

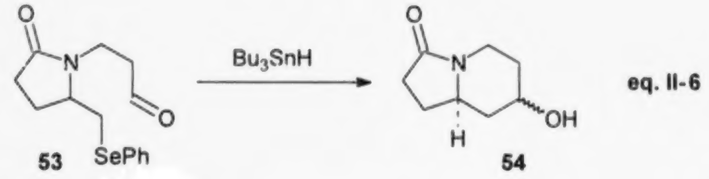
Scheme II-8

Jung[11] has used the formyl transfer reaction to advantage in synthetic work towards cyclophellitol. Exposure of aldehyde **51** to the conditions shown in eq. II-5 gave an 84% yield of the formyl transfer product **52**, which is an intermediate for the preparation of cyclophellitol.

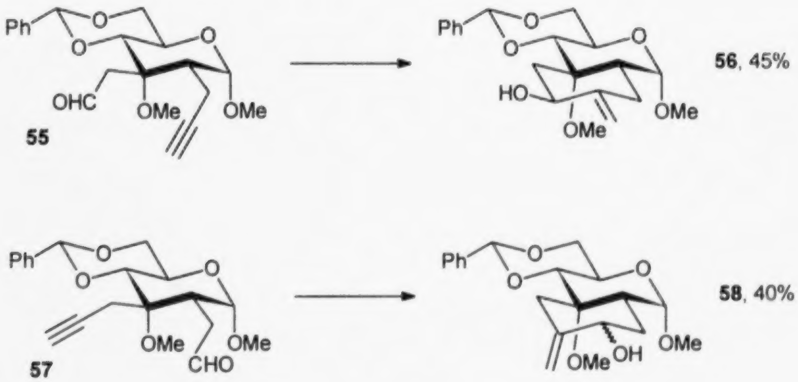

OBn
I
BnO
BnO
O
OHC
O
Ph
51
Bu$_3$SnH
[0.02M]
AIBN
PhH 3h
reflux
OBn
BnO
BnO
O
OHC
OBn
52

eq. II-5

Knapp[12] has found that 6-*exo* cyclization of **53** gave a 63% yield of alcohols **54** in a 3:2 ratio (eq. II-6).


Bu$_3$SnH
53
SePh
54
OH
H
eq. II-6

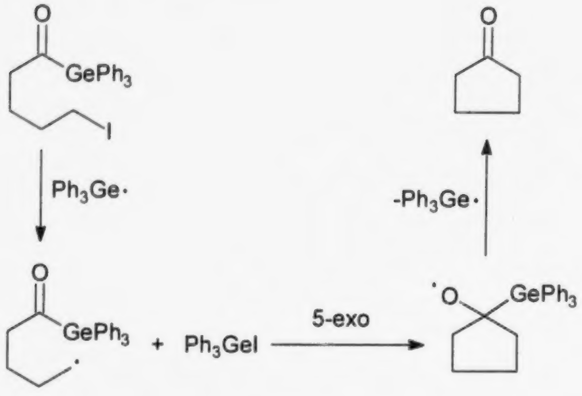
Addition of vinyl radicals (derived from stannylation of terminal alkynes) has also been studied (Scheme II-9).[10]


Ph
OHC
OMe
OMe
55
HO
OMe
OMe
56, 45%
Ph
OMe
OMe
CHO
57
OMe
OH
OMe
58, 40%

Scheme II-9

Other Carbonyl Acceptors

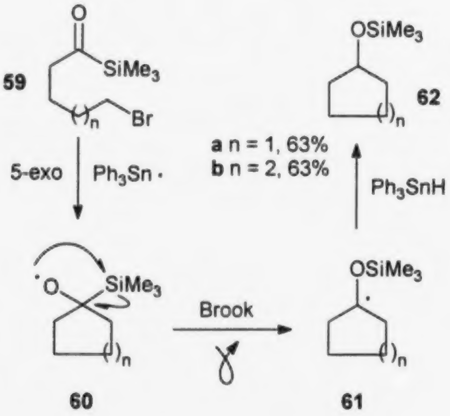
Although aldehydes have proven suitable as radical acceptors for the formation of six-membered rings there is always a constant search for the ideal acceptor that would serve well in both the 5-*exo* and 6-*exo* cyclizations. Having taken a lead from Kiyooka,[13] Curran[14] has developed a cyclization reaction onto an acyl germane that gives cyclic ketones (Scheme II-10).


O
GePh$_3$
I
Ph$_3$Ge·
O
GePh$_3$
+ Ph$_3$GeI
5-exo
·O
GePh$_3$
-Ph$_3$Ge·
O

Scheme II-10

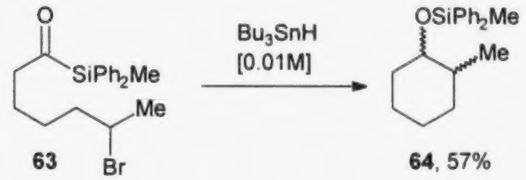
The acyl germane therefore acts a radical acceptor that gives ketones directly after radical cyclization. This is synthetically equivalent to addition to an aldehyde followed by oxidation of the resulting alcohol or addition to an acetylene followed by oxidative cleavage of the resultant olefin.

Tsai and Cherung[15] have found that acyl silanes also behave as suitable radical acceptors, but give the corresponding silyl ethers via a radical Brook rearrangement (**60**→**61**) (Scheme II-11).


59
O
SiMe$_3$
( )$_n$
Br
5-exo
Ph$_3$Sn ·
·O
SiMe$_3$
( )$_n$
60
Brook
61
OSiMe$_3$
( )$_n$
Ph$_3$SnH
a n = 1, 63%
b n = 2, 63%
OSiMe$_3$
( )$_n$
62

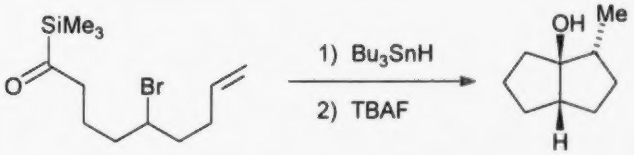
Scheme II-11

Formation of five membered and six-membered ring products proved to be a fairly efficient process since **62a** was isolated in 63% yield while **62b** was formed in 63% yield, both compounds being isolated as the benzoates. Secondary radicals also reacted in a similar fashion and it was found that the diphenylmethylsilyl derivative gave the highest proportion of cyclized product.[16]



63 **64**, 57% **eq. II-7**

An application of this closure to a tandem process was also examined[16] and the bicyclic structure **66** was formed in 81% yield (eq. II-8).

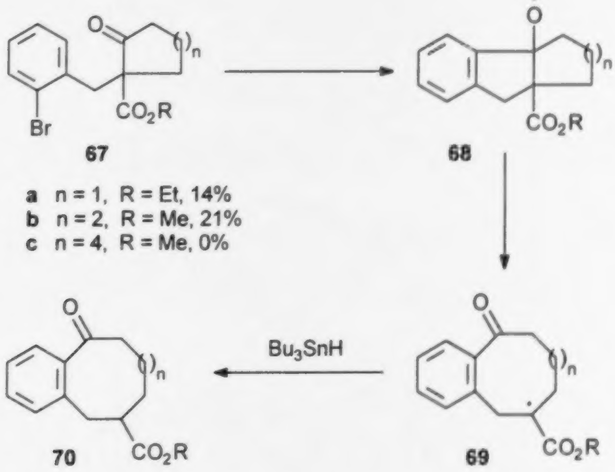


65 **66**, 81% **eq. II-8**

Radical Addition to Ketones Followed by Fragmentation

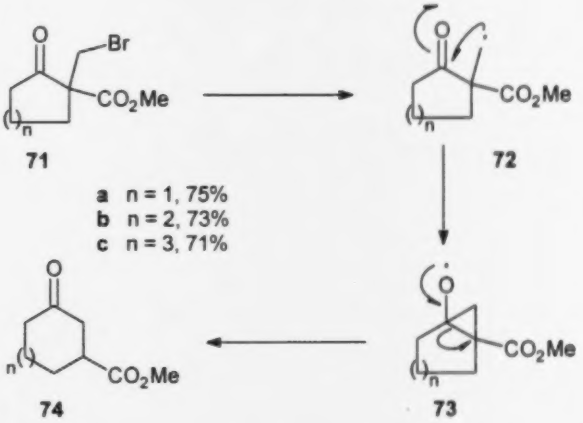
The radical addition to ketones is not efficient process unless an adjacent stabilizing group is present. In this case directed fragmentation of the formed alkoxy radical now becomes possible. In most cases the radical will collapse to a ketone and undergo rearrangement or ring expansion. This type of process has been used synthetically. Although this is a fairly new area a review[17] has appeared and this section will only highlight a few representative examples of these types of reactions.

The pioneering work of Beckwith[18] focused on the intramolecular addition of an aryl radical to an β-ketoester to give the intermediate alkoxy radical **68**, that then undergoes fragmentation to the ring expanded product **70** (Scheme II-12).


67
68
69
70
Br
CO2R
a n = 1, R = Et, 14%
b n = 2, R = Me, 21%
c n = 4, R = Me, 0%
Bu3SnH

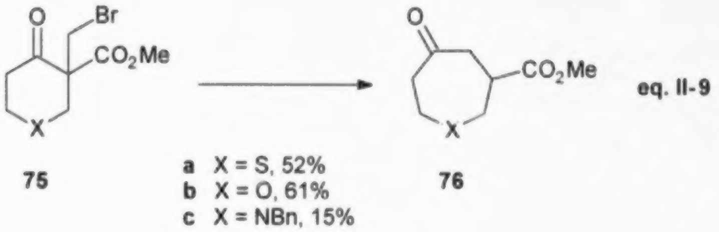
Scheme II-12

Work by Dowd and Choi[19] has resulted in a general strategy for the synthesis of various types of medium sized ring compounds (Scheme II-13).

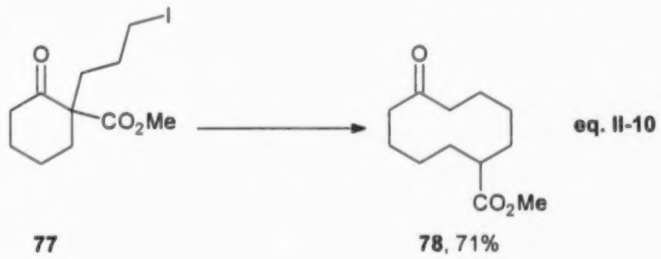

71
72
73
74
Br
CO2Me
a n = 1, 75%
b n = 2, 73%
c n = 3, 71%

Scheme II-13

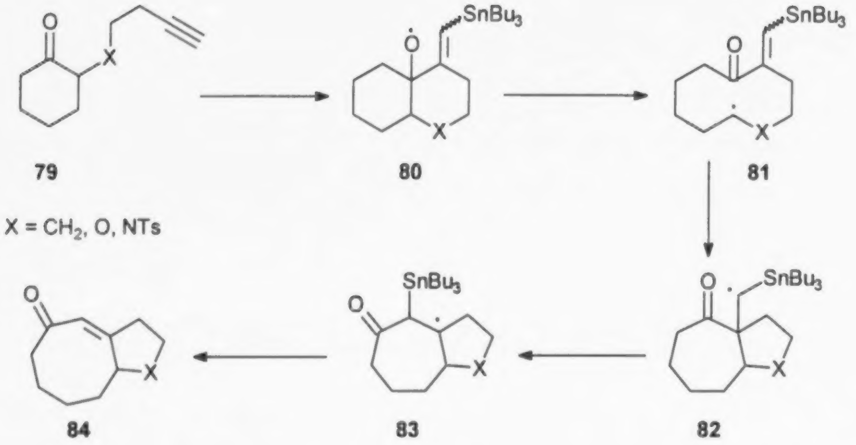
Medium sized heterocycles are also available by this technology (eq. II-9).[20]


Br
CO2Me
O
X
75
a X = S, 52%
b X = O, 61%
c X = NBn, 15%
76
eq. II-9

The radical source need not be only one carbon away, as shown in eq. II-10.[21]

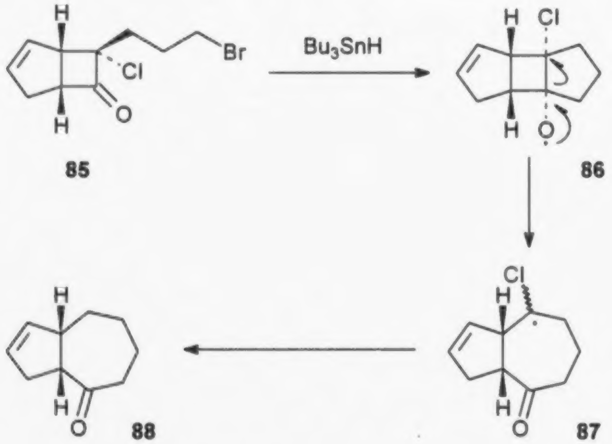

I
O
CO2Me
77
78, 71%
eq. II-10

An interesting application of this reaction is shown in Scheme II-14.[22] Where attack of a vinyl radical derived from acetylene **79** onto the carbonyl group causes ring expansion to **81** which is followed by a second ring expansion to **83**; the latter finally expels stannyl radical to form **84**.


79
X = CH2, O, NTs
80
81
82
83
84
SnBu3
X

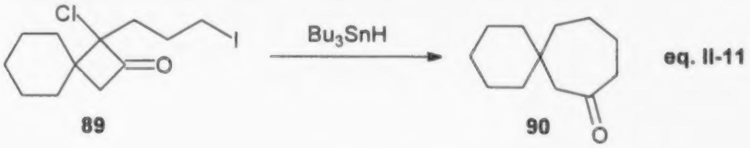
Scheme II-14

The cleavage of four-membered rings also opens the door to some interesting structures. Treatment of **85** with tributyltin hydride causes the carbon-bromine bond to be cleaved first. A primary radical is generated and it cyclizes onto the carbonyl group to give radical **86**. The chlorine atom serves to stabilize the radical thereby biasing cleavage of the cyclobutane ring as shown, to give the ring expanded product **88** (Scheme II-15).[23]


Bu3SnH
85
86
87
88
H
Cl
Br
O

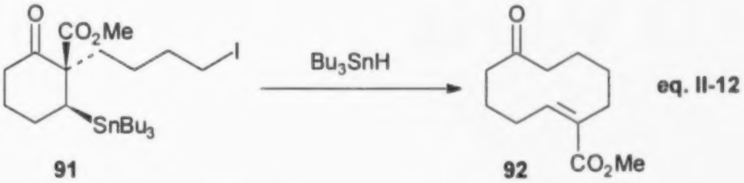
Scheme II-15

This same concept has also been applied to the formation of ring expanded spiro compounds (eq. II-11).[24]



89 **90**

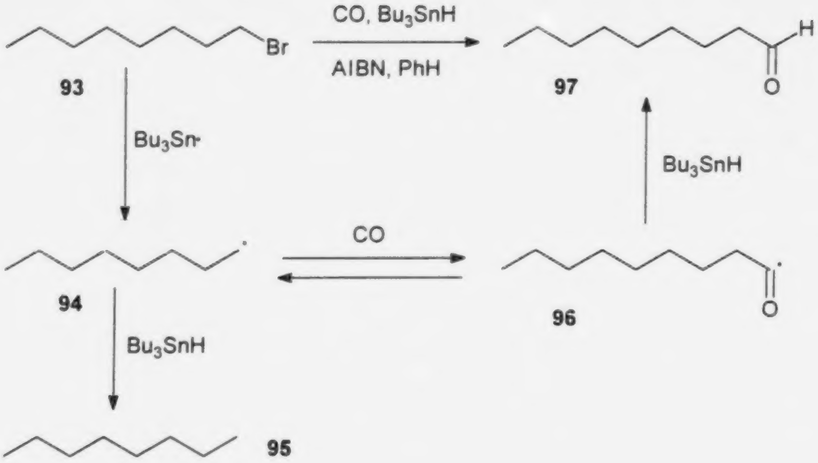
Work by Baldwin has also involved free radical ring expansion but in his case expulsion of stannane gives a ring expanded product containing an olefin (eq. II-12).[25]



91 **92**

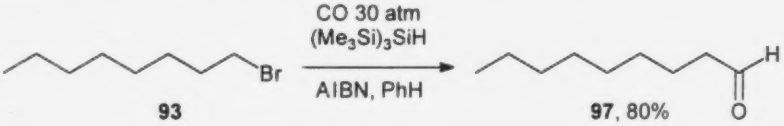
Radical Additions to Carbon Monoxide

Very recently the area of multi-component free radical additions to carbon monoxide and other heteroatomic acceptors (*eg.* isonitrile) has begun to grow rapidly and is due to the efforts of Sonoda, Ryu and co-workers. Early work[26] focused on the addition of alkyl radicals to CO under fairly high pressure to give aldehydes. The high pressure was necessary in order to favour reaction of the radical with carbon monoxide and not hydrogen abstraction from the tin hydride (Scheme II-16).


CO, Bu_3SnH
AIBN, PhH
Br
H
O
93
97
$Bu_3Sn\cdot$
Bu_3SnH
CO
94
96
Bu_3SnH
95

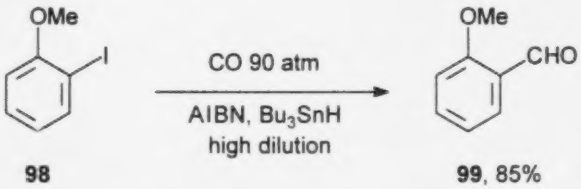
Scheme II-16

The pressure required to obtain a 66% yield of **97** is 80 atm. By switching to a poorer hydrogen atom donor it was possible to obtain an 80% yield of **97** by simply using tris(trimethylsilyl)silane as the hydride source at a pressure of 30 atm (eq. II-13).[27]


CO 30 atm
$(Me_3Si)_3SiH$
AIBN, PhH
Br
H
O
93
97, 80%

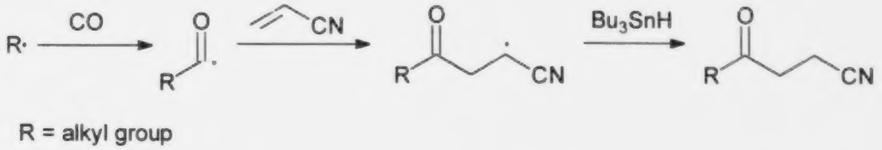
eq. II-13

The reaction is also applicable to aromatic substrates as shown by the example depicted in eq. II-14.[28]


OMe
I
CO 90 atm
AIBN, Bu_3SnH
high dilution
OMe
CHO
98
99, 85%

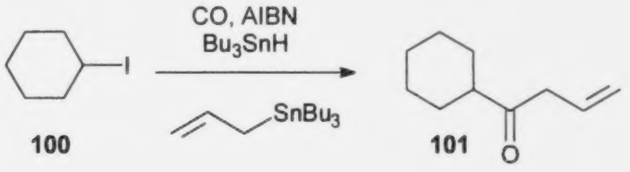
eq. II-14

Work from the same laboratories has resulted in an extension to a three component coupling terminating with addition to a Michael acceptor (Scheme II-17).[29]


R·
CO
CN
Bu$_3$SnH
R
O
CN
R = alkyl group

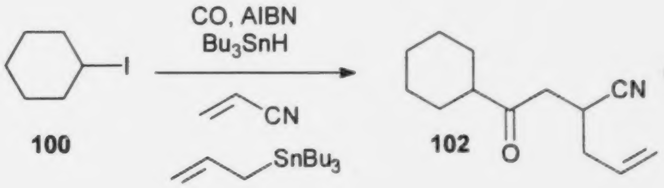
Scheme II-17

A similar three component reaction also worked well when an allylstannane was used as the radical terminator (eq. II-15).[30]


CO, AIBN
Bu$_3$SnH
SnBu$_3$
I
O
100
101

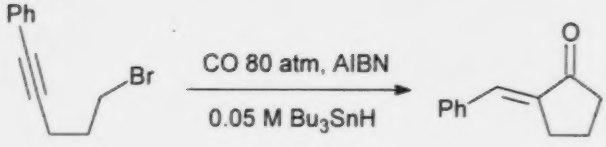
eq. II-15

A combination of the above two concepts finally led to the invention of a four component coupling reaction (eq. II-16).[31]


CO, AIBN
Bu$_3$SnH
CN
SnBu$_3$
I
O
CN
100
102

eq. II-18

The acyl radical has also been added to olefins in an intramolecular sense to synthesize cyclic ketones (eq. II-17).[32]


103

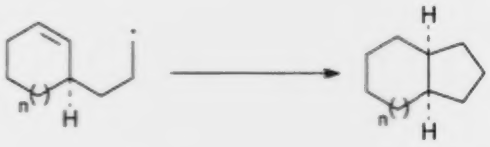
104

eq. II-17

The field of radical addition to carbonyl groups has generated some very exciting free radical chemistry and it is certain that this area will continue to yield new and interesting chemistry.

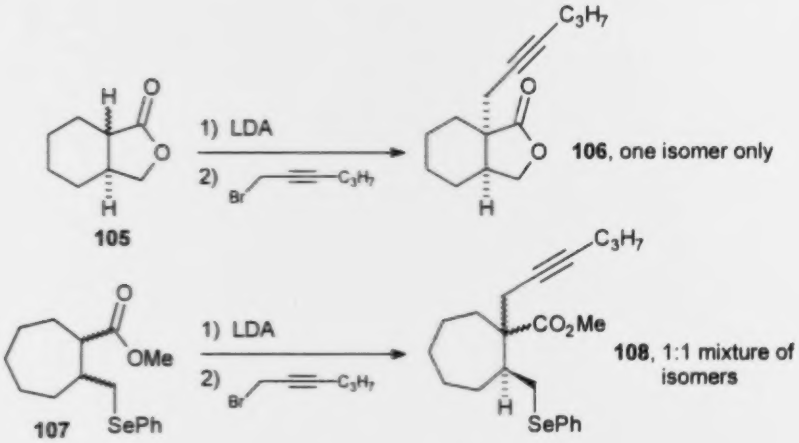
RESULTS and DISCUSSION

At the outset of this work we had the goal of constructing 6-membered *trans* ring-fused bicyclic compounds by an alkylation-radical cyclization route. The principle behind our method rests on the observation that radical cyclization of the type shown in eq. II-18 gives exclusively or mainly the *cis* ring-fused products.[33]



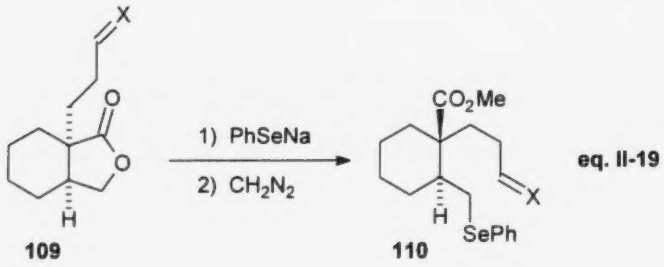
eq. II-18

In order to generate trans ring-fused products the last carbon-carbon bond formed must not be a bond to a ring fusion atom. It is therefore necessary to set-up two pendants attached to a ring–one carrying a radical source and the other carrying radical acceptor–*trans* to one another.


H
O
O
H
105
1) LDA
2) Br C₃H₇
C₃H₇
O
O
H
106, one isomer only
O
OMe
107
SePh
1) LDA
2) Br C₃H₇
C₃H₇
CO₂Me
H
SePh
108, 1:1 mixture of isomers

Scheme II-18

This type of system is available by alkylation of bicyclic lactones of type **105** (Scheme II-18). The alkylation has been shown[34] to proceed *syn* to the existing bridgehead hydrogen. If the alkylation is carried out on the related open chain benzeneseleno ester **107** then no selectivity is observed in the alkylation step. With the radical acceptor in place all that is now required is to introduce the radical source, and the lactone is rather well suited for this task. Ring opening with sodium phenyl selenide[35] followed by esterification of the resulting acid with diazomethane gives the requisite radical precursor **110** (eq. II-19).



Initially we chose to examine a 6-*endo* closure of a radical onto an α,β-unsaturated system. Previous work from these laboratories has shown that an electron withdrawing group on the olefin serves to increase the rate of 6-*endo* closure versus 5-*exo* closure to give mainly six-membered ring closure products (Scheme II-19).[36]

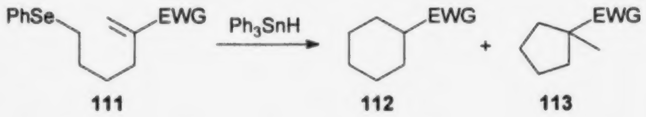
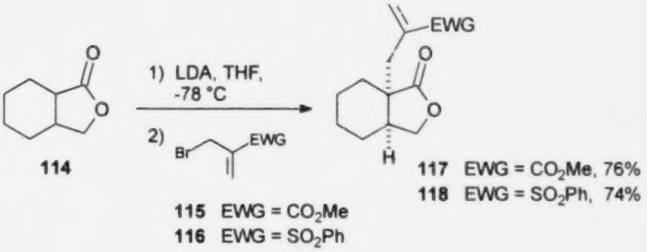


Table II-1 6-Endo versus 5-exo for 111

EWG	Yield	Yield
a CO_2Me	82%	12%
b CN	86%	4%
c SO_2Ph	84%	0%

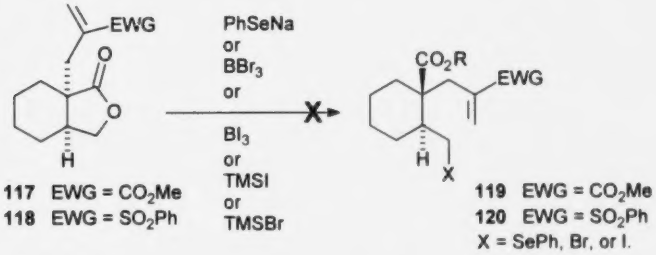
Scheme II-19

Compound **119** seemed to be an ideal target to test our hypothesis. Accordingly, alkylation of the enolate derived from lactone **114**[34] (by treatment with LDA at low temperature) with bromide **115**[37] gave a 76% yield of adduct **117**.


1) LDA, THF, -78 °C
2)
Br
EWG
O
O
EWG
O
O
H
114
115 EWG = CO$_2$Me
116 EWG = SO$_2$Ph
117 EWG = CO$_2$Me, 76%
118 EWG = SO$_2$Ph, 74%

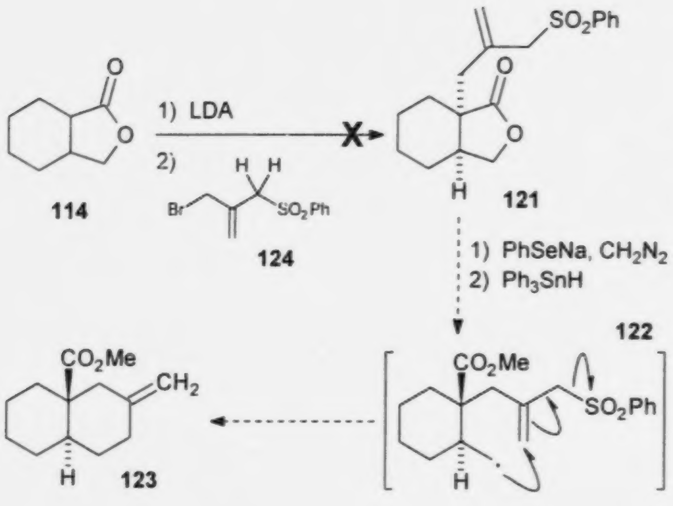
Scheme II-20

All attempts to open lactone ring of **117** to the radical precursors **119** or **120** via standard methods (PhSeNa,[35] BBr_3,[38] TMSBr, TMSI[39]) failed to provide the requisite radical precursors and gave only complex mixtures or recovered starting material. Similar results were encountered with the corresponding sulfone **118** that was made by alkylation with bromide **116**.[40]


EWG
O
O
H
117 EWG = CO$_2$Me
118 EWG = SO$_2$Ph
PhSeNa
or
BBr$_3$
or
BI$_3$
or
TMSI
or
TMSBr
CO$_2$R
EWG
H
X
119 EWG = CO$_2$Me
120 EWG = SO$_2$Ph
X = SePh, Br, or I.

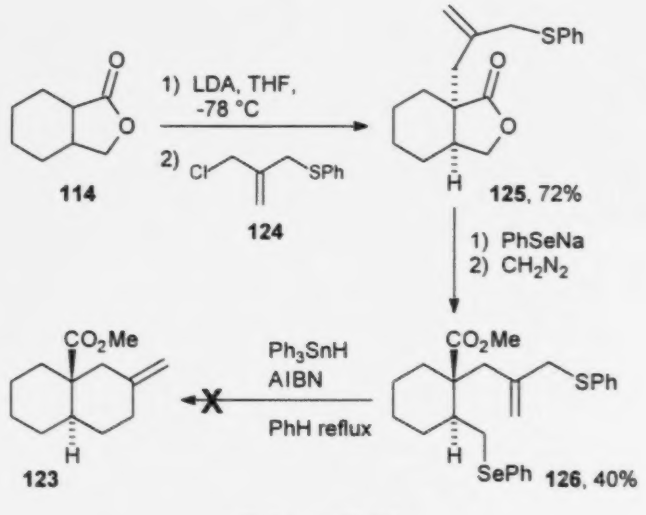
Scheme II-21

A different route was also examined in which the radical closure would involve an S_N2' type of addition[41] with elimination of $PhSO_2$ radical and the formation of an exocyclic double bond (Scheme II-22).


1) LDA
2)
H H
Br
SO2Ph
114
124
121
1) PhSeNa, CH2N2
2) Ph3SnH
122
CO2Me
CH2
SO2Ph
H
123

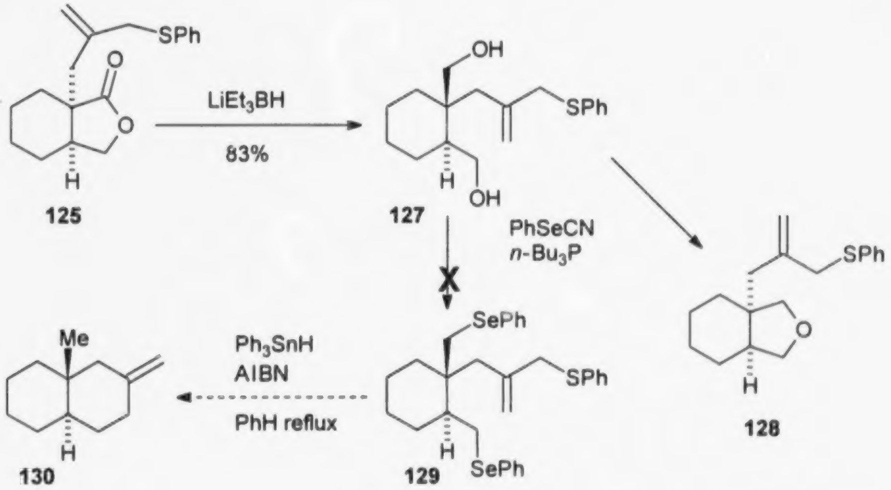
Scheme II-22

The alkylation step proved problematic since only recovered lactone was isolated from the reaction mixture. This is explained by assuming that the acidity of the protons between the sulfone function and double bond was sufficient to quench the enolate before alkylation could occur.


1) LDA, THF, -78 °C
2)
Cl
SPh
114
124
125, 72%
1) PhSeNa
2) CH2N2
CO2Me
Ph3SnH
AIBN
PhH reflux
SePh
126, 40%
H
123

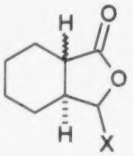
Scheme II-23

In order to circumvent this problem, we made the sulfide **125** by alkylation with the corresponding chloride. The sulfide underwent ring opening with sodium phenyl selenide to give **126** in low yield, but radical cyclization provided only recovered starting material (Scheme II-23). It then occurred to us that it may be possible to cyclize the ring and reduce the ester function to a methyl group in a limited number of operations. Accordingly, lactone **125** was reduced to diol **127**, but reaction with phenylseleno cyanate and *n*-tributylphosphine[42] gave only the tetrahydrofuran **128** instead of the desired diselenide **129** that should have been convertable to **130** by tin hydride mediated reduction (Scheme II-24).



Scheme II-24

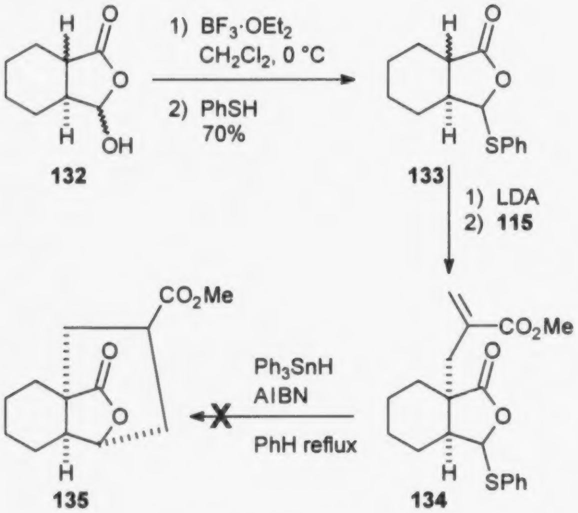
At this juncture it was clear that introduction of the radical precursor was troublesome. It was therefore decided that a structure of general type **131** may prove to be useful since only alkylation and the radical step would be required as the radical precursor is already in place. Our only worries were how to prepare this compound and we were not sure if the alkylation would still occur in the desired sense, *syn* to the bridgehead hydrogen atom.



131 Where X = SePh or SPh

Figure II-1

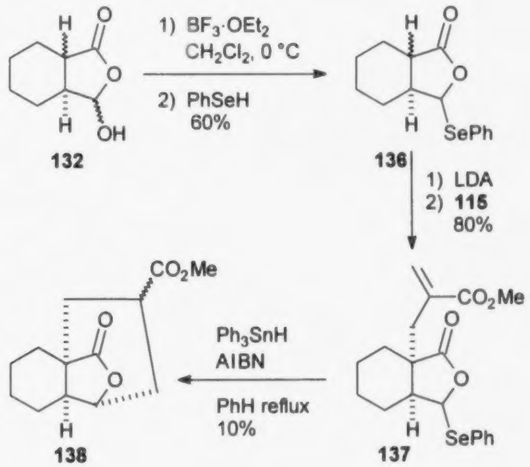
After some initial attempts,[43] we found that the thiolactal **133** could be prepared by analogy with procedures used in sugar chemistry. Thus, treatment of the lactal[44] with boron trifluoride etherate and thiophenol at 0°C in dichloromethane gave **133** as a single isomer in 70% yield.


1) BF3·OEt2
CH2Cl2, 0 °C
2) PhSH
70%
132
133
OH
SPh
1) LDA
2) 115
CO2Me
Ph3SnH
AIBN
PhH reflux
135
134
SPh

Scheme II-25

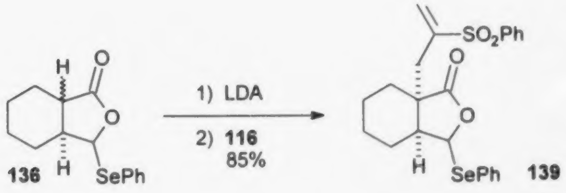
Alkylation proceeded in good yield to give a single isomer which we assumed to be the one shown above in Scheme II-25. All attempts (Ph_3SnH, AIBN, benzene reflux;

Ph_3SnH, Et_3B, hexane, air, RT; Ph_3SnH, AIBN, toluene reflux) to reductively cleave the sulfur-carbon bond via tin hydride methods in order to generate the requisite radical failed. Similar experiences have been encountered in these laboratories,[45] but related work by Marino[46] would seem to indicate that this reduction is indeed possible. This was not of concern since we made selenolactal **136** using analogous chemistry and alkylated it with **115**. However, exposure of the adduct **137** to radical conditions gave the product of 6-*endo* cyclization **138** as a mixture of isomers at the ester function in only 10% yield (Scheme II-26).


H
O
O
H
OH
132
1) BF3·OEt2
CH2Cl2, 0 °C
2) PhSeH
60%
H
O
O
H
SePh
136
1) LDA
2) 115
80%
CO2Me
O
O
H
138
Ph3SnH
AIBN
PhH reflux
10%
CO2Me
O
O
H
SePh
137

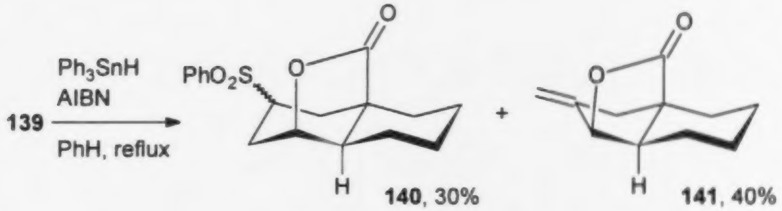
Scheme II-26

Changing the electron withdrawing group on the double bond to a sulfone opened the


H
O
O
136
H
SePh
1) LDA
2) 116
85%
SO2Ph
O
O
H
SePh
139

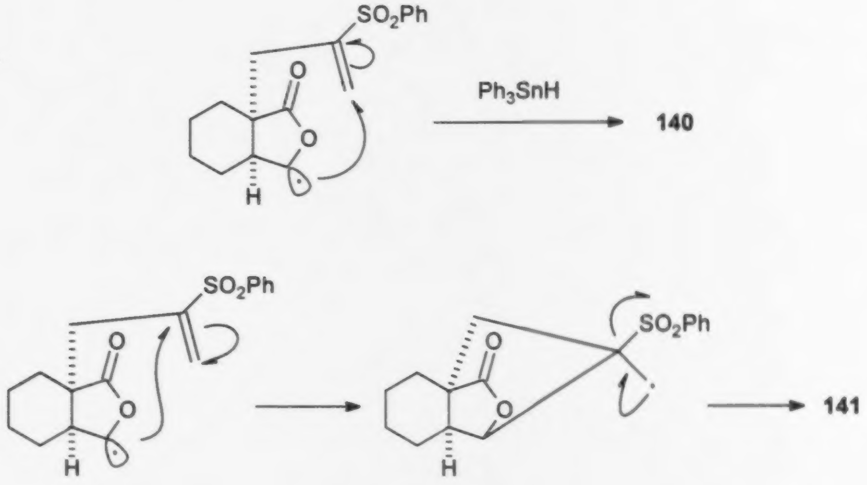
eq. II-20

door to some interesting results. Alkylation of **136** with bromide **116** gave an 85% yield of the adduct **139** as a single (undetermined) isomer. Exposure of **139** to standard radical conditions gave a mixture of two compounds **140** and **141** in 30% and 40% yield, respectively.


139
Ph_3SnH
AIBN
PhH, reflux
PhO_2S
O
O
H
140, 30%
+
O
O
H
141, 40%

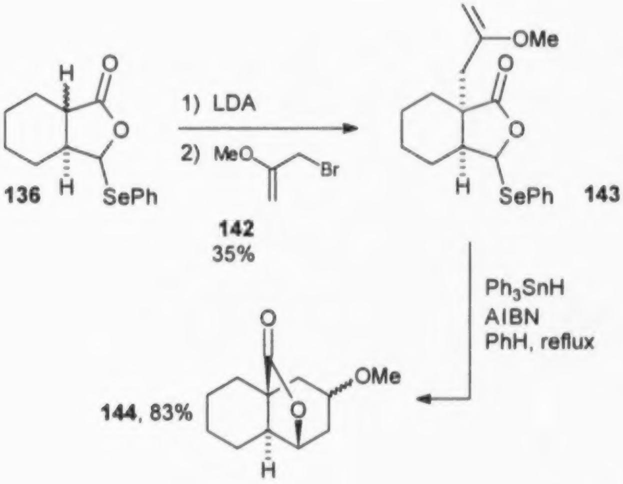
eq. II-21

The *trans*-decalin **140** arises from a 6-*endo* closure onto the double bond followed by tin hydride reduction of the resulting adduct radical. Compound **141** arises from 5-*exo* closure onto the olefin followed by extrusion of $PhSO_2$ radical and concomitant olefin formation (Scheme II-27).


SO_2Ph
O
O
H
Ph_3SnH
140
SO_2Ph
O
O
H
SO_2Ph
O
O
H
141

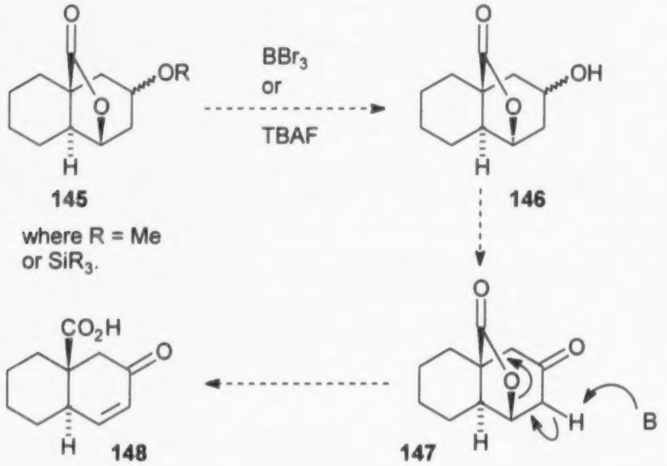
Scheme II-27

These results are rather surprising, since the sulfone is a strong electron withdrawing group and 5-*exo* closure should further be disfavored since that end of the olefin is disubstituted.[1e] Intuitively, we changed the nature of the group from electron withdrawing to electron donating in order to have an electron rich double bond to see if this would bias the system in favour of 6-*endo* closure. The substrate **143** was made by alkylation with the halide **142**[47] in low yield. This was in large part due to the instability of the enol ether to chromatography. Nevertheless a pure sample of **143** was exposed to thermal conditions for radical cyclization and an 83% yield of adduct **144** as a mixture of isomers was obtained (Scheme II-28).



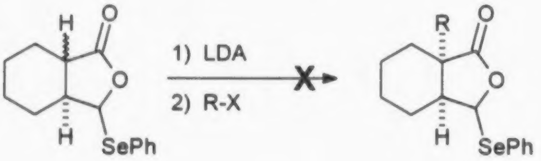
Scheme II-28

We were quite pleased with this result since it did indeed demonstrate that 6-*endo* closure is favored when electron donating groups are present on the double bond, a fact not previously appreciated. We also envisioned further use for adduct **144**, since it was conceivable that demethylation (or desilylation if we changed the nature of the olefin in the alkylation step) and oxidation of the resulting alcohol should furnish ketone **147**. Base induced elimination would then provide α,β-unsaturated ketone **148**, a compound that may prove useful for further chemistry (Scheme II-29).



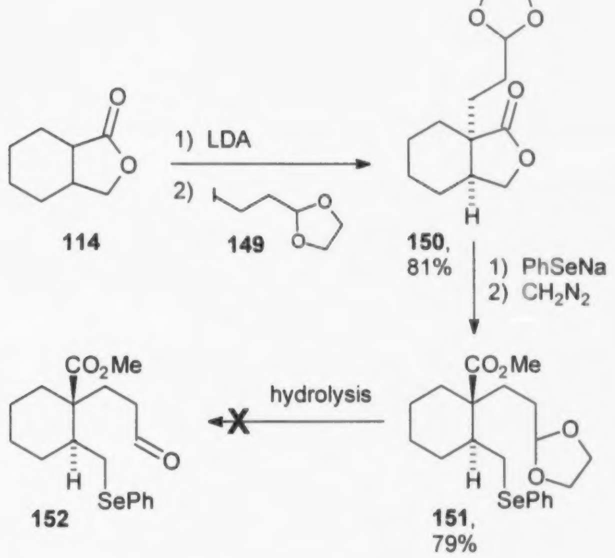
Scheme II-29

To our dismay we could not repeat the initial alkylation step. We tried various conditions as well as a few different electrophiles, but only decomposed starting material was isolated.



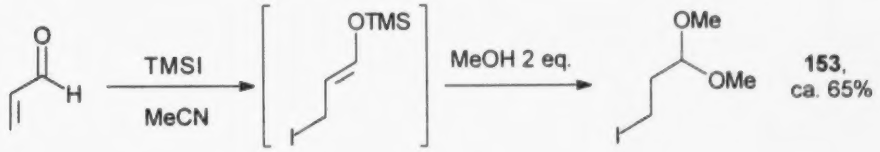
eq. II-22

Having been so close to success we were determined to find a system that would prove to be general for the requirements we initially outlined. It was then decided to retuirn to lactone **114** and examine the aldehyde function as a radical acceptor sinc eit has been shown to be a suitable radical acceptor. Accordingly, lactone **114** was alkylated with iodide **149**[48] to give a good yield of adduct **150**. Ring opening and esterification with diazomethane then gave the selenide ester **151** without incident. Unfortunately all attempts to hydrolyze the acetal function failed (Scheme II-30).


1) LDA
2)
114
149
150,
81%
1) PhSeNa
2) CH_2N_2
hydrolysis
152
151,
79%
CO2Me
H
SePh

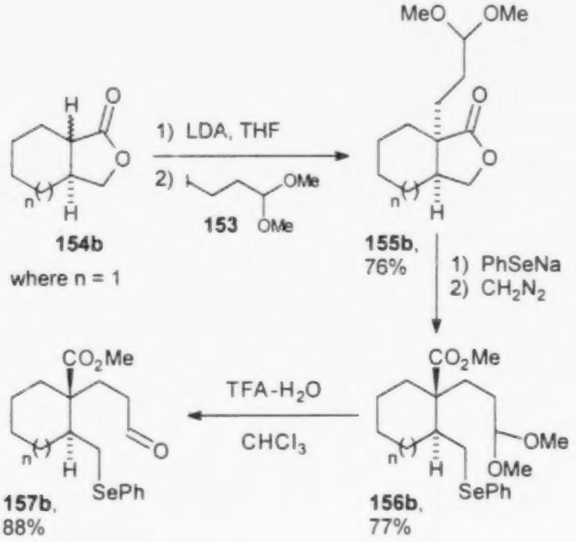
Scheme II-30

We then turned to the dimethyl acetal **155b**. It was made by alkylation of lactone **154b** with iodide **153** whose preparation is analogous to that of **149** and is shown in Scheme II-31.


TMSI
MeCN
OTMS
MeOH 2 eq.
OMe
OMe
153,
ca. 65%

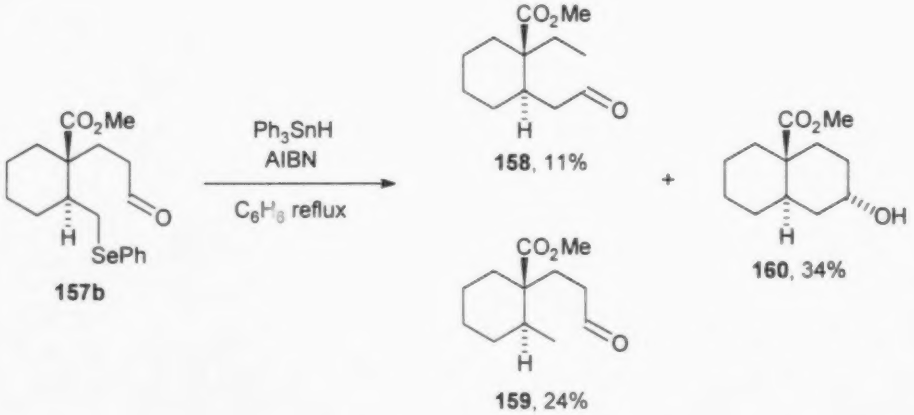
Scheme II-31

Ring opening gave **156b** which was found to be smoothly hydrolyzed (TFA-H_2O, $CHCl_3$)[49] to aldehyde **157b** in excellent yield (Scheme II-32).


MeO
OMe
H
O
O
1) LDA, THF
2)
OMe
153
OMe
n
H
154b
where n = 1
O
O
n
H
155b,
76%
1) PhSeNa
2) CH_2N_2
CO_2Me
TFA-H_2O
$CHCl_3$
n
H
O
SePh
157b,
88%
CO_2Me
n
H
OMe
OMe
SePh
156b,
77%

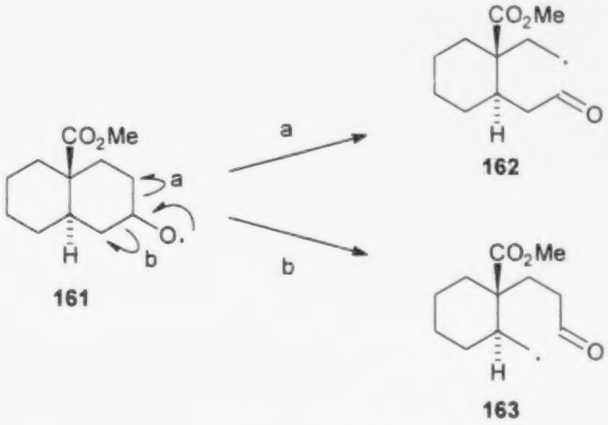
Scheme II-32

Exposure of **157b** to standard thermal conditions for radical generation (Ph_3SnH, AIBN, PhH reflux) gave a mixture of three compounds (Scheme II-33).


CO_2Me
H
O
SePh
157b
Ph_3SnH
AIBN
C_6H_6 reflux
CO_2Me
O
H
158, 11%
+
CO_2Me
OH
H
160, 34%
CO_2Me
O
H
159, 24%

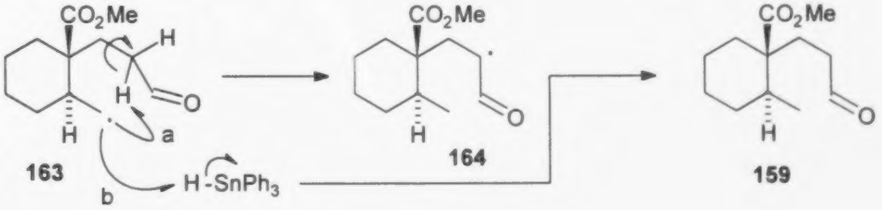
Scheme II-33

Compounds **158** and **159** may arise from reduction/fragmentation of the intermediate alkoxy radical **161**. While direct reduction of the alkoxy radical gives alcohol **160**.


CO₂Me
a
b
O·
H
161
162
163
CO₂Me
CO₂Me
H
H
O
O

Scheme II-34

There are two other possible pathways for the formation of **159**. Direct reduction of the initially formed carbon radical **163** by tin hydride (pathway b) or abstraction of hydride via a six-membered ring transition state to give the α-carbonyl radical **164** (pathway a) that would then be reduced to furnish the product **159** (Scheme II-35).


CO₂Me
H
H
O
H
a
b
163
H-SnPh₃
CO₂Me
H
164
O
CO₂Me
H
159
O

Scheme II-35

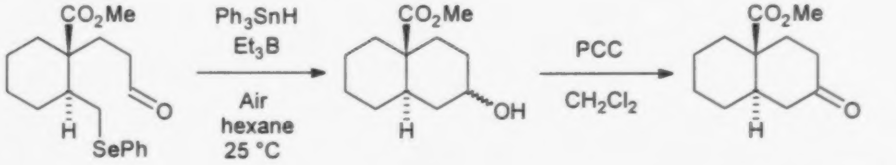
We then turned to the borane system for generating radicals. This involves the use of triethylborane in hexane at or below room temperature in the presence of oxygen.[50] The exact mechanism of the borane method is not known but the process is believed to follow the pathway illustrated in Scheme II-36. Attack of oxygen on the boron atom causes extrusion of ethyl radical that then reacts with tin hydride to give a stannyl radical which continues the chain process (Scheme II-36).

$$\mathrm{Et_2B\text{-}Et} \;+\; \cdot\mathrm{O{-}O}\cdot \;\longrightarrow\; \mathrm{Et}\cdot \;+\; \mathrm{Et_2BO\text{-}O}\cdot$$

$$\mathrm{Et}\cdot \;+\; \mathrm{Ph_3SnH} \;\longrightarrow\; \mathrm{C_2H_6} \;+\; \mathrm{Ph_3Sn}\cdot$$

Scheme II-36

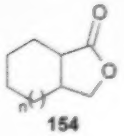
When the cyclization reaction was carried out with **157b** using the borane method a good yield of the cyclized product was obtained. It was found convenient to oxidize the crude alcohols directly to the corresponding ketone **166b** as it is more easily purified (Scheme II-37).



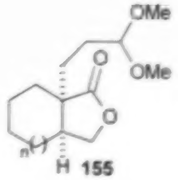
157b **165** **166b**, 73% over 2 steps

Scheme II-37

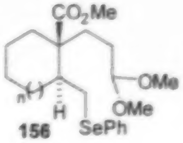
The reaction sequence is general as can be seen from the results listed in Table II-2 . The yields for the alkylation step are all good except for entry 1, in which formation of the enolate is probably disfavored due to the strain involved in the *cis* 5,5-ring-fused system. Selenide ring opening proceeded as expected, the only drawback being that in some cases starting lactone was recovered.



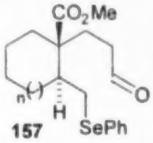
154



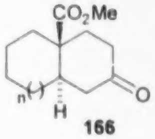
155



156



157



166

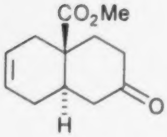
Table II-2[a] Alkylation Cylization Sequence of 157a-e

Entry	Lactone[b] **154**	Alkylated lactone **155**	Selenide **156**	Aldehyde **157**	Ketone[c] **166**
(i)	**154a** $n = 0$	**155a** $n = 0$, 40%	**156a** $n = 0$, 39%, (62%)[d]	**157a** $n = 0$, 86%	**166a** $n = 0$, 58%, (64%)[e, f]
(ii)	**154b** $n = 1$	**155b** $n = 1$, 76%	**156b** $n = 1$, 77%	**157b** $n = 1$, 88%	**166b** $n = 1$, 73%
(iii)	**154c** $n = 1$, $\Delta^{5,6}$	**155c** $n = 1$, $\Delta^{5,6}$, 71%	**156c** $n = 1$, olefin, 62%	**157c** $n = 1$, olefin, 95%	**166c** $n = 1$, olefin,[g] 71%
(iv)	**154d** $n = 2$	**155d** $n = 2$, 77%	**156d** $n = 2$, 50%	**157d** $n = 2$, 98%	**166d** $n = 2$, 80%
(v)	**154e** $n = 3$	**155e** $n = 3$, 63%	**156e** $n = 3$, 45%, (61%)	**157e** $n = 3$, 93%	**166e** $n = 3$, 77%

[a] All yields refer to pure compounds. [b] All lactones are saturated carbocycles except for n = 1, in which case both the saturated and $\Delta^{5,6}$ unsaturated [*i.e. cis*-3a,4,7,7a-tetrahydro-1-(3*H*)-isobenzofuranone] compounds were studied. [c] Overall yield for **157**→**166**. [d] Corrected for recovered starting lactone. [e] Corrected for recovered

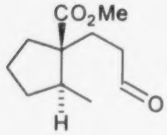
aldehyde **157a**. [f] Some reduced product (*i.e.* PhSe replaced by H) is also formed: 28% yield; 31% corrected for recovered starting material (**157a**, n = 0).

g



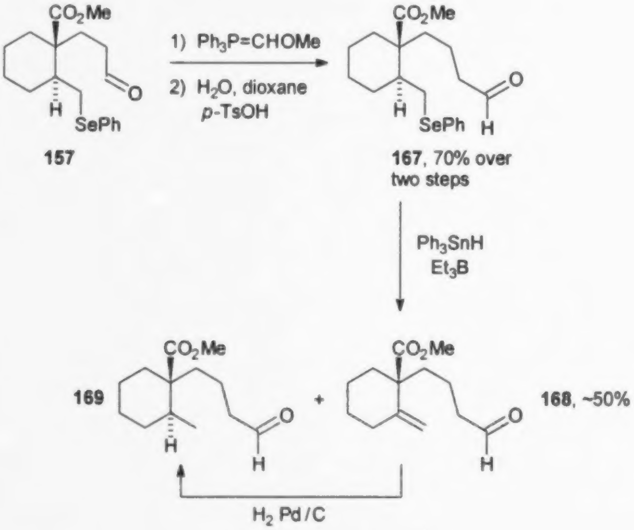
166c

h.



157a

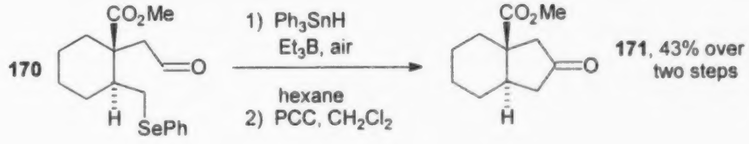
Since the yields of 6-membered ring products were good we were curious if this process was applicable to other ring sizes. We first examined a 7-*endo* cyclization to see if medium sized rings were accessible by this methodology.


CO2Me
SePh
H
157
1) Ph3P=CHOMe
2) H2O, dioxane
p-TsOH
167, 70% over two steps
Ph3SnH
Et3B
169
168, ~50%
H2 Pd/C

Scheme II-36

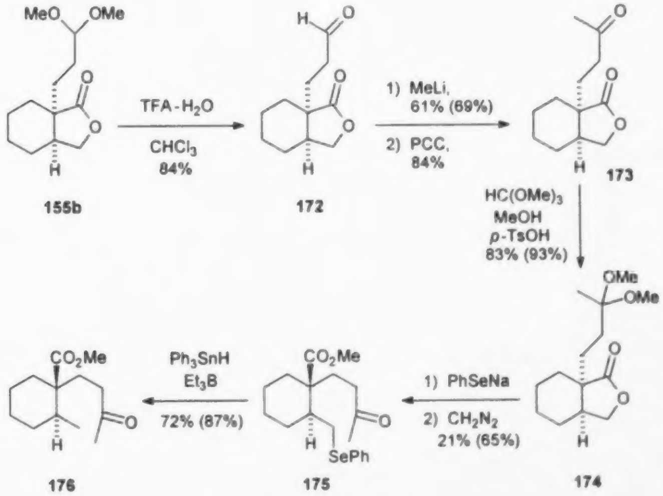
The requisite radical precursor **167** was made by Wittig chemistry,[51] and exposure of **167** to the borane conditions gave only the product of reduction **169** along with olefin **168**. Olefin **168** probably arises from a disproportionation reaction. Hydrogenolysis of **168** gave mainly **169** (Scheme II-36). Clearly, 7-membered ring formation was outside the scope of this process.

The next logical thing to do was to examine the disfavored 5-*exo* cyclization onto an aldehyde. The preparation of compound **170** is dealt with in Chapter 1 of this Thesis. Exposure of selenide **170** to triethyl borane conditions followed by oxidation gave a 43% of the ketone **171** (Equation II-23), while attempted cyclization under thermal conditions gave no cyclized product. This example shows that the borane method does effect cyclization in a case that does not proceed efficiently under thermal conditions.



170
CO_2Me
SePh
H
1) Ph_3SnH
Et_3B, air
hexane
2) PCC, CH_2Cl_2
CO_2Me
H
171, 43% over two steps

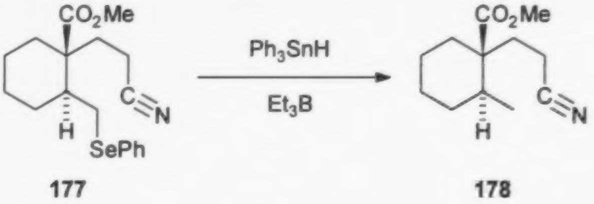
eq. II-23



MeO
OMe
155b
TFA-H_2O
$CHCl_3$
84%
172
1) MeLi, 61% (69%)
2) PCC, 84%
173
$HC(OMe)_3$
MeOH
p-TsOH
83% (93%)
OMe
OMe
174
1) PhSeNa
2) CH_2N_2
21% (65%)
CO_2Me
SePh
175
Ph_3SnH
Et_3B
72% (87%)
CO_2Me
176

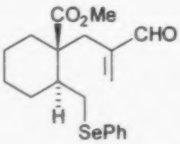
Scheme II-37

In order to determine the upper limit of this cyclization we also attempted radical cyclization onto a ketone. Aldehyde **172**, available from **155b** by hydrolysis, was treated with methyllithium and the resulting alcohols oxidized to ketone **173**. Ketalization to **174** was followed by ring opening with selenide that also deprotected the ketal to give a 21% yield of selenide **175** along with hydrolyzed starting material (Scheme II-37). Exposure of **175** to the borane conditions gave only the product of direct reduction **176**. The aldehyde function was the upper limit as a radical acceptor, but we have not yet examined cyclization onto esters. However, attempted cyclization of nitrile **177** (available from **157b** by oximation and dehydration) by the borane method gave only the product of reduction **178** and recovered starting material (eq. II-24).



eq. II-24

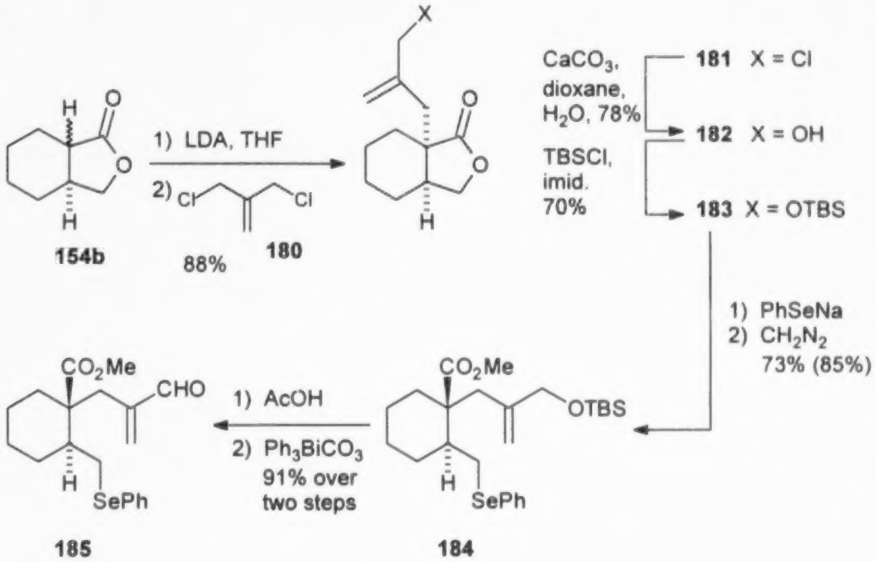
Curiosity generated from our work in 6-*endo* cyclizations left us wondering if we could set-up a system that would allow direct competition between a 6-*exo* trigonal cyclization onto an aldehyde and a 6-*endo* trigonal cyclization onto the double bond of an α,β-unsaturated system. Compound **179** seemed perfectly suited for our needs (Figure II-2).



179

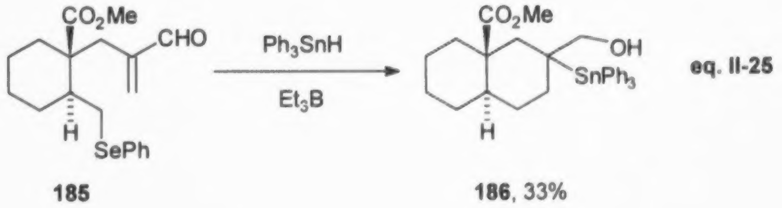
Figure II-2

It was prepared by alkylation of lactone **154b** with dichloride **180**.[52] Conversion of the chloride into the silyl ether was followed by ring opening and esterification to provide **184**. Desilylation and oxidation then furnished **185** (Scheme II-38).

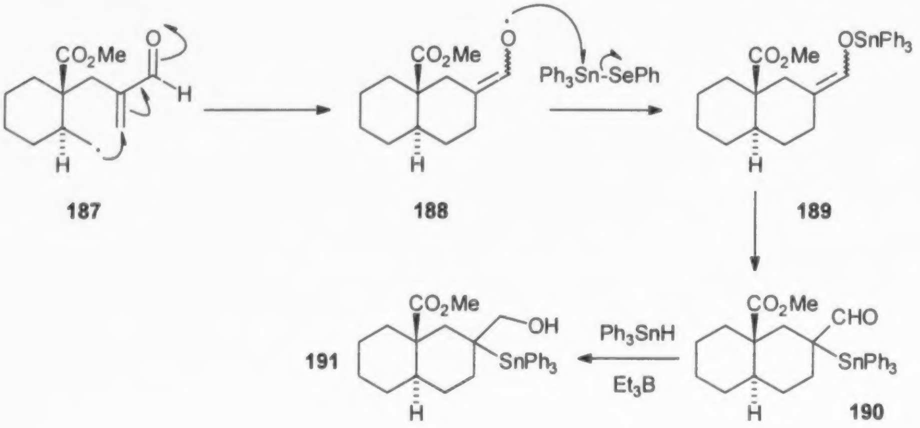

154b
1) LDA, THF
2) Cl Cl
180
88%
X
CaCO₃, dioxane, H₂O, 78%
TBSCl, imid. 70%
181 X = Cl
182 X = OH
183 X = OTBS
1) PhSeNa
2) CH₂N₂
73% (85%)
CO₂Me
OTBS
SePh
184
1) AcOH
2) Ph₃BiCO₃
91% over two steps
CHO
185

Scheme II-38

Exposure of **185** to the borane conditions for radical cyclization resulted in the formation of alcohol **186**.


CO₂Me
CHO
SePh
185
Ph₃SnH
Et₃B
OH
SnPh₃
186, 33%
eq. II-25

A possible mechanism for its formation is shown below in Scheme **II-39**. A fast 6-*endo* cyclization is followed by capture of the radical **188** with tin to give the stannyl enol ether **189** which undergoes a tin O→C shift[53] to give **190**. Triethyl borane-tin hydride mediated reduction[53] of the aldehyde then furnished the alcohol **191**.



Scheme II-39

It seems that reduction of the aldehyde function by tin hydride and triethyl borane is a potential problem in this methodology, but obviously for aldehyde **157**, closure is much faster the carbonyl reduction. In the above case, reduction probably occurs after cyclization since at that point the molecule has little else to react with. The above example shows that in the above system, 6-*endo* cyclization is faster than 6-*exo* closure onto a carbonyl group.

There are several differences between the thermal method and the borane method. In the thermal method the reaction is conducted at 80 °C and the initiator and stannane are added slowly over ten hours to ensure that premature reduction of the initially formed selenide is minimized. When we followed the conditions outlined by Fraser-Reid[7] for cyclization of ω-iodo-aldehydes, we obtained significant amounts of reduction/fragmentation products. In the borane method the reaction is carried out at a lower temperature (25°C) and the triphenyltin hydride and triethyl borane are added in one portion at the beginning of the experiment. We suspect that not only does the triethyl borane act as a radical initiator, but it also has the potential to function as a Lewis acid and complex the aldehyde oxygen thereby weakening the π-bond and facilitating radical addition (Figure II-3).

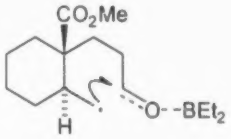
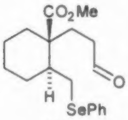
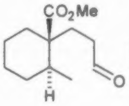


Figure II-3

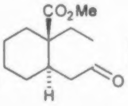
In order to gain more insight into the reasons of why the borane method was working so well, we decided to carry out a series of experiments and some of the results we obtained are listed in Table II-3.



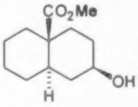
157b



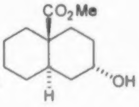
159



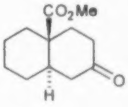
158



192



193



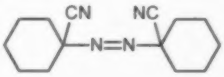
166b

Table II-3[a] Various Conditions for Cylization of 157b

Entry	Conditions	159	158	192	193	166b
(i)	Ph_3SnH, Et_3B,hexane, 25 °C, air	–[b]	–[b]	–[e]	–[e]	73%[c]
(ii)	Ph_3SnH, AIBN, C_6H_6, 80 °C	24%[d]	11%[d]	–	34%[d]	–[f]
(iii)	Ph_3SnH, Et_3B,hexane, 0 °C, air	–	–	–[e]	–[e]	39%[d, c]

(iv)	Ph_3SnH, Et_3B, C_6H_6, 80 °C	26%[d]	–	–[e]	–[e]	43%[c, d]
(v)	Ph_3SnH, $Ti(OPr\textit{i})_4$, C_6H_6, 80 °C	–	–	–[e]	–[e]	11%[c, d]
(vi)	Ph_3SnH, initiator[g], C_6H_6, 80 °C	28%	–	3%	22%	–[f]
(vii)	Ph_3SnH, initiator[h], hυ (Hg) C_6H_6, 10 °C	–	–	–e	–e	32%[c](49%)[d]
(viii)	Ph_3SnH, sunlamp, hυ C_6H_6, 10 °C	20%	-	32%	47%	-[f]

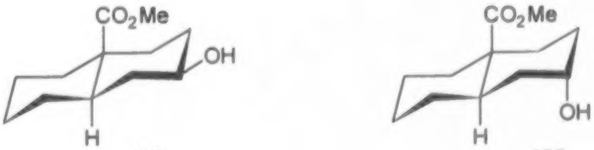
[a] Yields refer to isolated compounds. [b] Only a trace if any. [c] Yield over two steps (cyclization and oxidation). [d] Yield corrected for recovered starting material. [e] Oxidation carried out directly. [f] Experiment not tried. [g]



[h] *t*-Bu-N=N-*t*-Bu

The first two entries serve to contrast the borane method and the thermal method. It is clear that the borane method is superior to the thermal method for radical cylization onto aldehydes. Lowering the temperature (entry iii) did not improve the yield, but little if any reduction/fragmentation was observed. However, in several of these reactions starting material was recovered. Entry iv illustrates the use of triethyl borane as a Lewis acid, in the absence of oxygen, and the yield is acceptable, but some reduction product was also isolated. The use of titanium isopropoxide as a Lewis acid gave only a low yield of cyclized product (after oxidation). Two different initiators (entries vi and vii) were also examined and it seems that this did not improve the efficiency of our method. The last entry is rather interesting. Reaction with triphenyltin hydride and the use of a sunlamp as the initiator gave a 79% combined yield of alcohols. The reaction was very clean and this allowed us to fully characterize the products. The lower temperature employed may be the reason for the lack of fragmentation since cyclization is favored over fragmentation at lower temperatures due to entropic factors. The absence of an initiator is somewhat unique since hexaalkyditins are frequently used under photolysis conditions, but it would seem from this result that an initiator is not always required. This reaction is interesting and more study is required to explore the generality of this mild method of carbon-carbon bond formation.

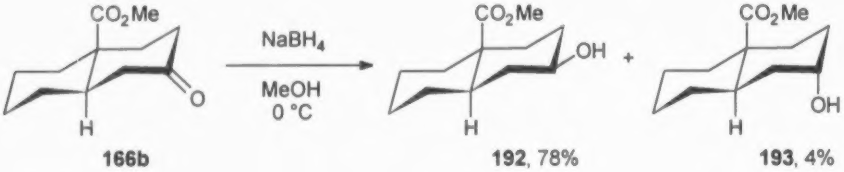
For completeness, we needed to assign the stereochemistry of the adduct alcohols obtained from radical cyclization of compound **157b**. ^{13}C NMR spectroscopy was used initially since it is known that the chemical shift of the carbinol carbon of equatorial alcohols absorbs at higher ppm than axial alcohols.[54]



192 **193**

Figure II-4

The chemical shift of the carbinol carbon for the major product from radical cyclization for both the thermal and borane method was 66.66 ppm while the minor product had a resonance at 70.80 ppm and on this basis we assigned the major product from radical cyclization as being the axial alcohol **193** and the minor the equatorial alcohol **192** (Figure II-4). In order to confirm our assignment it was decided to resort to a chemical method. Sodium borohydride reduction of ketone **166b** in methanol at 0°C gave **192** as the major product (78%) with a small amount of **193** (4%) (eq. II-26). This corresponds to an axial delivery of hydride[55] from the bottom face of the decalin ring system. Chelation controlled delivery of hydride by the ester can be ruled out since the solvent would highly solvate the borohydride species making ester chelation highly improbable.[55]

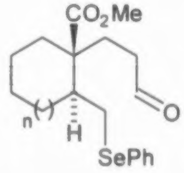


eq. II-26

CONCLUSION

It has been shown that radical cyclization of alkyl selenides of the type **157** leads effciently to the corresponding six-membered ring alcohols by the use of the triethyl borane method. It would seem that the cyclization process is favored by carrying out the reaction at lower tempertures (below 25°C).

157

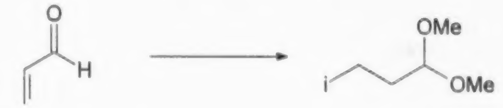


where n = 0, 1, 2, and 3.

Figure II-5

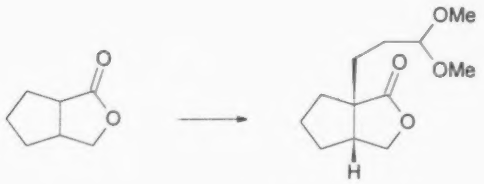
EXPERIMENTAL

1,1-Dimethoxy-3-iodopropane (153).



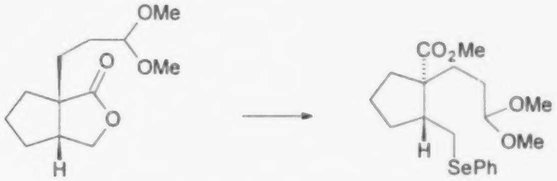
The literature procedure for the corresponding ethylene ketal[48] was followed with some modifications. Freshly distilled Me_3SiCl (15.3 mL, 120 mmol) was added over 1 min to a stirred and cooled (0°C) solution of acrolein (6.7 mL, 100 mmol) and dry NaI (18 g, 120 mmol) in dry MeCN (250 mL). The resulting yellow solution was stirred for 5 min and then dry MeOH (9.72 mL, 240 mmol) was added in one portion. Stirring was continued for 5 min and the solution was then poured onto 5% saturated aqueous $NaHCO_3$ (100 mL) overlaid with pentane (300 mL). The mixture was shaken and bottom layer was removed and the remaining two organic phases were washed with 5% aqueous $Na_2S_2O_3$ (80 mL) and then with brine (7 x 100 mL) at which point only the top layer remained. The organic extract was dried (K_2CO_3) and evaporated. The residual oil was dissolved in pentane (20 mL) and filtered through a short column of basic alumina (3 x 8 cm), using pentane (100 mL) as eluent. The filtrate was evaporated to give **153** (13.9 g, 60%) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2988, 2952, 2935, 2908, 2830, 1458, 1443 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04-2.11 (m, 2 H), 3.12 (t, $J = 7$ Hz, 2 H), 3.31, (s, 6 H), 4.42 (t, $J = 5.5$ Hz, 1 H); ^{13}C NMR APT (100.6 MHz, $CDCl_3$) δ -0.14 (t'), 36.47 (t'), 53.51 (q'), 104.42 (d'). A suitable combustion analysis couild not be obtained.

cis-6a-(3,3-Dimethoxypropyl)hexahydro-1-_H_-cyclopenta[c]furan-1-one (155a).



$(Me_3Si)_2NLi$ was prepared by rapid addition (ca. 30 sec) of _n_-BuLi (5.67 mL, 1.6 M in hexane, 9.07 mmol) to a stirred and cooled (-78 °C) solution of bis(trimethylsilyl)amine (1.91 mL, 9.07 mmol) in THF (30 mL). The mixture was stirred for 15 min and then a solution of lactone **154a** (1.0402 g, 8.25 mmol) in THF (10 mL plus 2 mL as a rinse) was added by cannula over 1 min. The resulting solution was stirred for 15 min, and then iodide **153** (2.50 g, 10.9 mmol) was added neat in one portion. The cooling bath was left in place and stirring was continued overnight, during which time the mixture attained room temperature. The reaction was quenched with cold saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 30 mL). The combined ethereal extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the resulting yellow oil over silica gel (3 x 20 cm), using 20% Et_2O-hexane, gave **155a** (0.7584 g, 40%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^1H NMR (400 MHz)] oil: FT-IR ($CDCl_3$ cast) 2940, 1762, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.80 (br m, 8 H), 1.85-1.94 (m, 1 H), 2.04-2.11 (m, 1 H), 2.51-2.59 (m, 1 H), 3.24 (s, 3 H), 3.26 (s, 3 H), 3.85 (dd, J = 10, 3.5 Hz, 1 H), 4.24-4.35 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 25.19 (t'), 28.64 (t'), 31.16 (t'), 34.32 (t'), 37.92 (t'), 43.37 (d'), 52.68 (q'), 53.09 (q'), 54.75 (s'), 72.64 (t'), 104.16 (d'), 182.34 (s'); exact mass, _m/z_ calcd for $C_{12}H_{20}O_4$ [$(M - H^+)^+$] 227.1283, found 227.1281. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.99; H, 9.09.

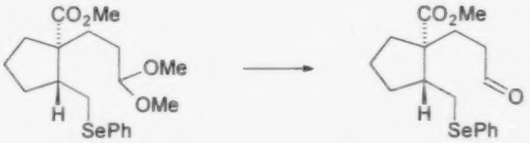
Methyl *cis*-1-(3,3-dimethoxypropyl)-2-[(phenylseleno)methyl]cyclopentanecarboxylate (156a).



A literature procedure[35] for cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (6 mL) was added to a mixture of PhSeSePh (702.3 mg, 2.25 mmol) and NaH (162.0 mg, 60% dispersion in oil, 14.16 mmol) and the resulting slurry was refluxed for 30 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry, degassed HMPA (1.0 mL) was added. The precipitate dissolved, and a solution of lactone **155a** (684.3 mg, 3.00 mmol) in THF (10 mL plus 3 mL as a rinse) was added via cannula, and the mixture was refluxed for 10 h. It was cooled to room temperature, quenched with MeOH (3 mL), acidified (litmus red) by addition of cold (4°C) HCl (0.5M, 10 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and evaporated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **156a**. Evaporation of the Et_2O and flash chromatography of the crude product over silica gel (3 x 23 cm), using EtOAc-hexane mixtures (6 to 30% EtOAc), gave unreacted lactone **155a** (256.1 mg, 37%), and then selenide **156a** (467.5 mg, 39%, 62% corrected for recovered **155a**) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^1H NMR (400 MHz)] yellow oil: FT-IR ($CHCl_3$ cast) 2949, 1724, 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.32 (m, 1 H), 1.43-1.69 (br m, 5 H), 1.78-1.89 (m, 1 H), 1.95-2.11 (m, 3 H), 2.22-2.30 (m, 1 H), 2.56 (t, J = 12 Hz, 1 H), 3.15 (dd, J = 12, 3.15 Hz, 1 H), 3.28 (s, 3 H), 3.30 (s, 3 H), 3.68 (s, 3 H), 4.32 (t, J = 6 Hz, 1 H), 7.20-7.29 (m, 3 H), 7.44- 7.49

(m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.91 (t'), 28.74 (t'), 29.63 (t'), 31.24 (t'), 32.55 (t'), 33.80 (t'), 50.89 (d'), 51.36 (q'), 52.17 (q'), 52.78 (q'), 57.09 (t'), 104.28 (d'), 126.65 (d'), 128.96 (d'), 130.51 (s'), 132.22 (d'), 175.54 (s'); exact mass, *m/z* calcd for $C_{19}H_{28}O_4Se$ 400.1153, found 400.1152. Anal. Calcd for $C_{19}H_{28}O_4Se$: C, 57.14; H, 7.07. Found: C, 57.07; H, 6.94.

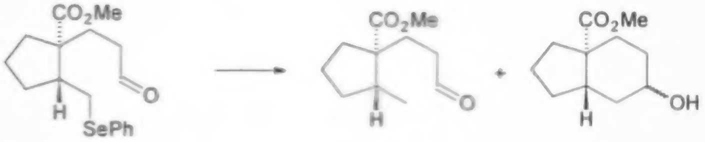
Methyl *cis*-1-(3-oxopropyl)-2-[(phenylseleno)methyl]cyclopentanecarboxylate (157a).



A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 30 mL) was added to a solution of acetal **156a** (437.5 mg, 1.10 mmol) in $CHCl_3$ (40 mL) and the resulting heterogeneous mixture was stirred vigorously for 12 h at room temperature. The mixture was then cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 20 mL), brine (1 x 10 mL), dried, and concentrated. Flash chromatography of the resulting yellow oil over silica gel (2 x 18 cm), using 10% EtOAc-hexane, gave aldehyde **157a** (339.2 mg, 87%) as a pure [^{1}H NMR, (400 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 2950, 1478, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.70 (br m, 4 H), 1.80-1.90 (m, 1 H), 1.99-2.14 (m, 2 H), 2.33-2.43 (m, 2 H), 3.11 (dd, *J* = 12, 3 Hz, 1 H), 3.68 (s, 3 H), 7.20-7.30 (m, 3 H), 7.45-7.50 (m, 2 H), 9.71 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.06 (t'), 29.45 (t'), 29.68 (t'), 31.42

(s'), 34.11 (t'), 40.64 (t'), 50.96 (d'), 51.54 (q'), 56.57 (t'), 126.85 (d'), 129.03 (d'), 130.25 (s'), 132.42 (d'), 175.24 (s'), 201.36 (d'); exact mass, *m/z* calcd for $C_{17}H_{22}O_3Se$ 354.0734, found 354.0727. Anal. Calcd for $C_{17}H_{22}O_3Se$: C, 57.79; H, 6.28. Found: C, 58.13; H, 6.12.

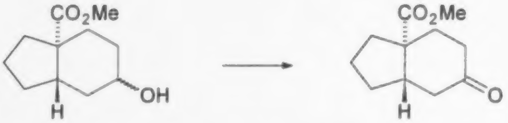
Methyl *cis*-2-methyl-1-(3-oxopropyl)cyclopentanecarboxylate (194), Methyl (3aα , 7aβ)-octahydro-6α-hydroxy-3a*H*-indene-3a-carboxylate (195), and Methyl (3a α, 7aβ)-octahydro-6β-hydroxy-3a*H*-indene-3a-carboxylate (196).



Ph_3SnH (442.3 mg, 1.26 mmol) in hexane (4 mL plus 1 mL rinse) and Et_3B (1M solution in hexane, 2.0 mL, 2.0 mmol) were added simultaneously to a solution of aldehyde **157a** (144.1 mg, 0.401 mmol) in hexane (80 mL) over 15 sec. Air (20 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued for 4 h. At this point the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (1 M solution in hexane, 0.88 mL, 0.88 mmol) were added, and stirring was continued. The above process was repeated once more after 3 h, and stirring was then continued for 8 h. Evaporation of the reaction mixture and flash chromatography of the crude product over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (10 to 30% EtOAc), gave unreacted selenide **157a** (15.2 mg, 10.5%), reduced starting material **194** (22.2 mg, 28%, 31% corrected for recovered starting material) as a pure [^{1}H NMR (400 MHz)], clear oil and the epimeric alcohols **195** and **196** which were directly oxidized to ketone **166a** without characterization. Compound **194** had: FT-IR (CH_2Cl_2 cast) 2954, 2873, 1723, 1451

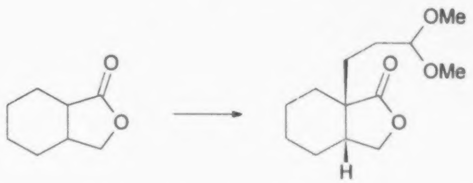
cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.8 Hz, 3 H), 1.30-1.45 (m, 2 H), 1.48-1.63 (m, 2 H), 1.72-1.86 (m, 3 H), 2.11-2.24 (m, 2 H), 2.32-2.45 (m, 2 H), 3.61 (s, 3 H), 9.71 (t, J = 1.5 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 15.93 (q'), 22.49 (t'), 29.85 (t'), 33.21 (t'), 33.40 (t'), 41.01 (t'), 45.53 (d'), 51.16 (q'), 56.32 (s'), 175.91 (s'), 201.88 (d'); exact mass, *m/z* calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1243.

Methyl (3aα, 7aβ)-octahydro-6-oxo-3a*H*-indene-3a-carboxylate (166a).



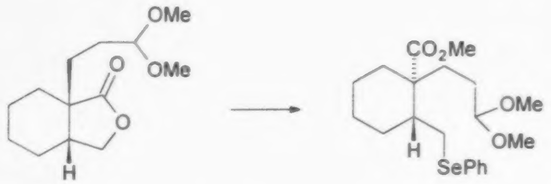
PCC (260.0 mg, 1.20 mmol) and crushed 4Å molecular sieves (100 mg) were added to a solution of alcohols **195** and **196** in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature under argon for 10 h, then filtered through a pad of Celite:$MgSO_4$::4:1 (1 x 8 cm), using CH_2Cl_2 (70 mL), and the eluent was evaporated. Flash chromatography of the crude product over silica gel (2 x 16 cm), using EtOAc-hexane mixtures (7 to 20% EtOAc), gave ketone **166a** (45.4 mg, 58% from **157a**, 64% based on recovered selenide **157a**) as a pure [TLC silica, 30% EtOAc-hexane, ^{1}H NMR, (400 MHz)], clear oil: FT-IR (CH_2Cl_2 cast) 2953, 2874, 1713, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.45 (m, 1 H), 1.46-1.59 (m, 1 H), 1.53-1.93 (m, 5 H), 2.05-2.66 (m, 1 H), 2.25-2.52 (m, 4 H), 2.68-2.77 (m, 1 H), 3.66 (s, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.56 (t'), 22.75 (t'), 35.11 (t'), 35.96 (t'), 38.50 (t'), 42.87 (t'), 48.68 (d'), 51.56 (q'), 52.59 (s'), 175.33 (s'), 210.92 (s'); exact mass, *m/z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1097. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.22.

cis-7a-(3,3-Dimethoxypropyl)hexahydro-1(3*H*)-isobenzofuranone (155b).



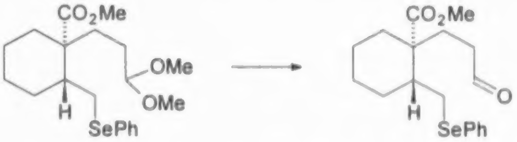
LDA was prepared by the rapid additon (ca. 60 sec) of *n*-BuLi (17.1 mL, 1.6M in hexane, 27.36 mmol) to a magnetically stirred and cooled (ice-bath) solution of *i*-Pr_2NH (3.84 mL, 27.4 mmol) in THF (40 mL). The solution was then cooled to -78°C and, after an additional 10 min, a solution of lactone **154b** (7.40 g, 29.9 mmol) in THF (17 mL plus 4 mL as a rinse) was added by cannula over 1 min. The resulting solution was stirred for 20 min and then iodide **153**(7.40 g, 29.9 mmol) was added neat in one portion. The cold bath was removed and stirring was continued for 12 h. Cold saturated aqueous NH_4Cl (5 mL) was added and the solution was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (7 x 20 cm), using 8% EtOAc-hexane, gave **155b** (4.5878 g, 76%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^1H NMR (200 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 2933, 2859, 2890, 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23-2.00 (br m, 12 H), 2.18-2.35 (m, 1H), 3.29 (s, 6H), 3.89-4.01 (m, 1H), 4.20-4.35 (m, 2H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 21.84 (t'), 22.14 (t'), 25.36 (t'), 27.13 (t'), 29.15 (t'), 29.40 (t'), 38.73 (d'), 44.58 (s'), 52.85 (q'), 52.99 (q'), 69.32 (t'), 104.45 (d'), 180.40 (s'); exact mass, *m/z* calcd for $C_{13}H_{22}O_4$ $[(M - H^+)]^+$ 241.1439, found 241.1439. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.75; H, 9.09.

Methyl *cis*-1-(3,3-dimethoxypropyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (156b).



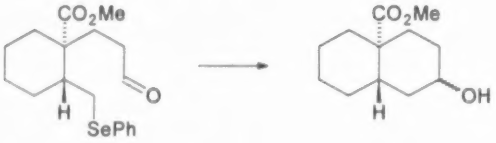
A literature procedure[35] for the cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (10 mL) was added to a mixture of PhSeSePh (2.4565 g, 10.49 mmol) and NaH (566.4 mg, 60% dispersion in oil, 14.16 mmol) and the resulting slurry was refluxed for 45 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry HMPA (1.0 mL) was added. The precipitate dissolved, and a solution of lactone **155b** (2.5409 g. 10.49 mmol) in THF (10 mL plus 2 mL as a rinse) was added by cannula, and the mixture was refluxed for 24h. It was cooled to room temperature, quenched with MeOH (6 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 10 mL), and extracted with EtOAc (3 x 45 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **156b**. Evaporation of the ether and flash chromatography of the crude product over silica gel (7 x 20 cm),using EtOAc-hexane mixtures (4 to 15% EtOAc), gave **156b** (3.3520 g, 77%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (200 MHz)], yellow oil: FT-IR ($CHCl_3$ cast) 2937, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23-2.00 (br m, 13 H), 2.90-3.15 (m, 2 H) 3.28 (s, 3 H), 3.29 (s, 3 H), 4.38 (t, J = 5.2 Hz, 1 H), 7.20-7.35 (m, 3 H), 7.46-7.57 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 22.05 (t'), 22.82 (t'), 26.06 (t'), 26.95 (t'), 29.33 (t'), 29.91 (t'), 30.95 (t') 43.80 (d'), 49.89 (t'), 51.18 (q'), 52.28 (q'), 52.70 (q'), 104.30 (d'), 126.69 (d'), 128.83 (d'), 130.62 (s'), 132.74 (d'), 176.15 (s'); exact mass, *m/z* calcd for $C_{20}H_{30}O_4Se$ 414.1309, found 414.1333. Anal. Calcd for $C_{20}H_{30}O_4Se$: C, 58.10; H, 7.31; O, 15.48. Found: C, 58.17; H, 7.37; O, 15.64.

Methyl *cis*-1-(3-oxopropyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (157b).



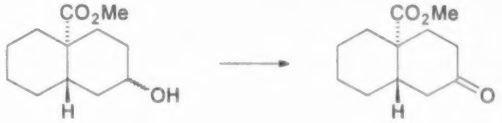
A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 30 mL) was added to a solution of acetal **156b** (3.3520 g, 8.11 mmol) in $CHCl_3$ (60 mL) and the resulting heterogeneous mixture was stirred vigorously for 16 h at room temperature. The mixture was then cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 35 mL). The combined organic extracts were washed with saturated sodium bicarbonate (1 x 25 mL), brine (1 x 15 mL), dried, and concentrated. Flash chromatography of the crude product over silica gel (4 x 23 cm), using 15% EtOAc-hexane, gave **157b** 2.6229 g (88%) as a pure [^{1}H NMR (200 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 2935, 2860, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-2.13 (br m, 11 H), 2.20-2.34 (m, 2 H), 2.89-3.15 (m, 2 H), 3.65 (s, 3 H), 7.22-7.36 (m, 3 H), 7.49-7.60 (m, 2 H), 9.68 (t, $J = 1.3$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 22.14 (t'), 23.08 (t'), 26.31 (t'), 28.22 (t'), 29.87 (t'), 30.19 (t'), 38.78 (d'), 43.98 (d'), 49.59 (s'), 51.50 (q'), 127.07 (d'), 129.05 (d'), 130.49 (s'), 133.24 (d'), 175.81 (s'), 201.11 (d'); exact mass, *m/z* calcd for $C_{18}H_{24}O_3Se$ $[(M\text{-}H)]^+$ 368.0890, found 368.0888. Anal. Calcd for $C_{18}H_{24}O_3Se$: C, 58.85; H, 6.59. Found: C, 58.92; H, 6.63.

Methyl (4aβ, 8aα)-decahydro-2α-hydroxynaphthalene-4a-carboxylate (193) and Methyl (4aβ, 8aα)-decahydro-2β-hydroxynaphthalene-4a-carboxylate (192)



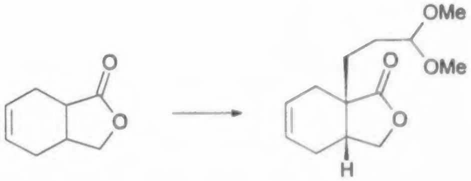
Ph_3SnH (540.0 mg, 1.538 mmol) in hexane (4 mL plus 1 mL rinse) and Et_3B (2.6 mL, 1M in hexane, 2.6 mmol) were added simultaneously to a solution of aldehyde **157b** (430.2 mg, 1.171 mmol) in hexane (25 mL) over 20 sec. Air (20 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued for 7 h. At this point the reaction was still incomplete (TLC, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (1 M solution in hexane, 1.0 mL, 1.0 mmol) were added, and stirring was continued for 6 h. Evaporation of the solvent and flash chromatography of the crude product over silica gel (3 x 20 cm), using 10% EtOAc-hexane, gave the epimeric alcohols **192** and **193** (240 mg, 96% combined yield). The major isomer (**193**; axial hydroxyl (^{13}C NMR 75.5 MHz) was fully characterized: FT-IR (CH_2Cl_2 cast) 3400 (broad), 1729 cm^{-1}; ^1H NMR ($CDCi_3$, 200 MHz) δ 1.05-1.89 (br m, 14 H), 1.95-2.20 (m, 2 H), 3.65 (s, 3 H), 4.11 (br t, $J = 2.5$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 23.62 (t'), 26.62 (t'), 28.90 (t'), 30.27 (t'), 31.77 (t'), 36.53 (t'), 38.25 (t'), 38.37 (d'), 48.69 (s'), 51.11 (q'), 66.63 (d'), 176.03 (s'); exact mass, *m/z* calcd for $C_{12}H_{20}O_3$ $[(M - H^+)]^+$ 211.1334, found 211.1335. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.43; H, 9.69. The minor isomer **192** was not characterized, but was oxidized directly along with **193** to ketone **166b**.

Methyl (4aβ, 8aα)-decahydro-3-oxo-naphthalene-4a-carboxylate (166b).



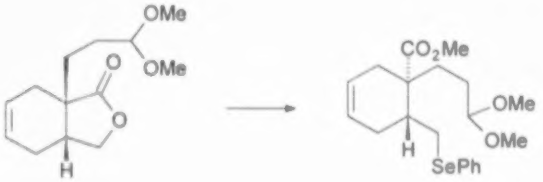
PCC (780 mg, 3.60 mmol) and powdered 4 Å molecular sieves (100 mg) were added to a stirred solution of alcohols **192** and **193** in CH_2Cl_2 (10 mL). Stirring under argon was continued for 3 h and the mixture was then filtered through Celite (3 x 10) cm. The pad was washed with CH_2Cl_2 (15 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 5% EtOAc-hexane, gave ketone **166b** (181.4 mg, 74%) as a clear homogeneous [2D-TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (200 MHz)], oil : FT-IR (CH_2Cl_2 cast) 2926, 2858, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz] δ 1.06-1.96 (br m, 9 H), 2.09-2.40 (m, 5 H), 2.85-3.04 (m, 1 H), 3.71 (s, 3 H); ^{13}C NMR APT ($CDCl_3$, 74.469 MHz) δ 23.36 (t'), 25.74 (t'), 29.20 (t'), 37.22 (t'), 37.35 (t'), 39.20 (t'), 44.70 (d'), 45.37 (t'), 47.51 (s'), 51.63 (q'), 175.12 (q'), 210.76 (q'); exact mass, *m/z* calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1255. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.89.

cis-3a,4,7,7a-Tetrahydro-7a-(3,3-dimethoxypropyl)-1(3*H*)-isobenzofuranone (155c).



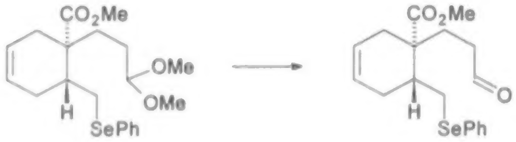
LDA was prepared by rapid additon (*ca.* 60 sec) of *n*-BuLi (16.01 mL, 1.6M in hexane, 24.02 mmol) to a magnetically stirred and cooled (ice-bath) solution of *i*-Pr_2NH (3.37 mL, 24.02 mmol) in THF (45 mL). The solution was then cooled to -78 °C and, after an additional 10 min, a solution of lactone **154c** (3.0171 g, 21.83 mmol) in THF (10 mL plus 3 mL as a rinse) was added by cannula over 1 min. The resulting solution was stirred for 30 min and then *n*-BuLi (5.00 ml, 1.6M in hexane, 8.00 mmol) was added and the solution stirred for 10 min at -78°C, at which point iodide **153** (7.40 g, 29.9 mmol) was added neat in one portion. The cold bath was removed and stirring was continued for 12 h. Cold saturated aqueous NH_4Cl (5 mL) was added and the solution was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (6 x 20 cm), using EtOAc-hexane mixtures (6 to 20% EtOAc), gave **155c** (3.7240 g, 71%) as a pure [^{1}H NMR, (200 MHz)] oil: FT-IR (CH_2Cl_2 cast) 2935, 1770, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49-1.71 (br m, 4 H), 1.89-2.02 (m, 2 H), 2.17-2.33 (m, 2 H), 2.50-2.60 (m, 1 H), 3.25 (s, 3 H), 3.27 (s, 3 H), 3.85 (t, $J = 4$ Hz, 1 H), 4.21-4.32 (m, 2 H), 5.65-5.78 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.08 (t'), 27.32 (t'), 29.15 (t'), 30.17 (t'), 36.30 (d'), 43.21 (s'), 52.68 (q'), 53.02 (q'), 70.11 (t'), 104.38 (d'), 124.40 (d'), 124.83 (d'), 181.07 (s'); exact mass, *m/z* calcd for $C_{13}H_{20}O_4$ 239.1283, found 239.1289. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.06; H, 8.32.

Methyl *cis*-1-(3,3-dimethoxypropyl)-2-[(phenylseleno)methyl]-3-cyclohexenecarboxylate (156c).



A literature procedure[35] for the cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (6 mL) was added to a mixture of PhSeSePh (849.0 mg, 3.63 mmol) and NaH (196.0 mg, 60% dispersion in oil, 4.90 mmol) and the resulting slurry was refluxed for 60 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry, degassed HMPA (1.0 mL) was added. The precipitate dissolved, and a solution of lactone **155c** (873.6 mg, 3.63 mmol) in THF (5 mL plus 2 mL as a rinse) was added by cannula, and the mixture was refluxed for 18 h. It then was cooled to room temperature, quenched with MeOH (2 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 7 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **156c**. Evaporation of the Et_2O and flash chromatography of the crude product over silica gel (4 x 21 cm), using 6% EtOAc-hexane, gave selenide **156c** (926.4 mg, 62%) as a pure [^{1}H NMR, (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2947, 1728, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29-1.40 (m, 1 H), 1.52-1.70 (m, 3 H), 2.00-2.10 (m, 1 H), 2.19-2.45 (m, 4 H), 2.74 (t, J = 12 Hz, 1 H), 2.80-2.86 (m, 1 H), 3.28 (s, 3 H), 3.29 (s, 3 H), 3.60 (s, 3 H), 4.28 (t, J = 5 Hz, 1 H), 5.54-5.65 (m, 2 H), 7.22-7.31 (m, 3 H), 7.47-7.55 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 25.91 (t'), 27.26 (t'), 27.38 (t'), 30.08 (t'), 30.41, (t'), 39.25 (d'), 48.43 (s'), 51.55 (q'), 52.47 (q'), 52.65 (q'), 104.26 (d'), 123.92 (d'), 124.29 (d'), 126.84 (d'), 128.95 (d'), 130.40 (s'), 132.74 (d'), 176.27 (s'); exact mass, *m/z* calcd for $C_{20}H_{28}O_4Se$ 412.1153, found 412.1156. Anal. Calcd for $C_{20}H_{28}O_4Se$: C, 58.39; H 6.86. Found: C, 58.26; H, 6.92.

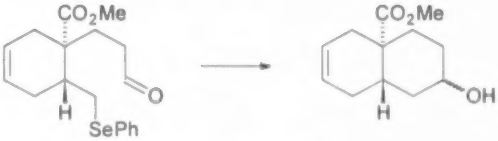
Methyl *cis*-1-(3-oxopropyl)-2-[(phenylseleno)methyl]-3-cyclohexenecarboxylate (157c).



A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 15 mL) was added to a solution of acetal **156c** (405.1 mg, 0.985 mmol) in $CHCl_3$ (30 mL) and the resulting heterogeneous mixture was stirred vigorously for 16 h at room temperature. The mixture was then cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were washed with saturated saqueous $NaHCO_3$ (1 x 20 mL), brine (1 x 15 mL), dried, and concentrated. Flash chromatography of the crude product over silica gel (3 x 23 cm), using 10% EtOAc-hexane, gave aldehyde **157c** (340.1 mg, 95%) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2948, 1726, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88-2.05 (m, 3 H), 2.20-2.35 (m, 3 H), 2.37-2.50 (m , 3 H), 2.70-2.86 (m, 2 H), 3.59 (s, 3 H), 5.56-5.66 (m, 2 H), 7.25-7.33 (m, 3 H), 7.49-7.56 (m, 2 H), 9.71 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 25.76 (t'), 27.17 (t'), 27.35 (t'), 29.68 (t'), 38.91 (d'), 39.03 (t'), 47.90 (s'), 51.61 (q'), 123.91 (d', I assume two signals are coincident), 126.68 (d'), 128.69 (d'), 130.13 (s'), 132.79 (d'), 175.72 (s'), 200.83 (d'); exact mass, *m/z* calcd for

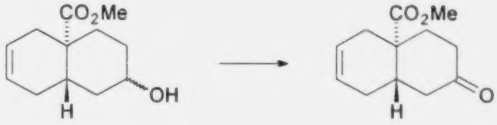
$C_{18}H_{22}O_3Se$ 366.0734, found 366.0742. Anal. Calcd for $C_{18}H_{22}O_3Se$: C, 59.18; H, 6.07. Found: C, 58.97; H, 6.05.

Methyl (4aα, 8aβ)-1,2,3,4,4a,5,8,8a-octahydro-2β-hydroxynaphthalene-4a-carboxylate (197) and Methyl (4aα, 8aβ)-1,2,3,4,4a,5,8,8a-octahydro-2α-hydroxynaphthalene-4a-carboxylate (198)



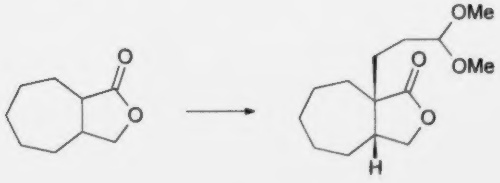
Ph_3SnH (160.0 mg, 0.452 mmol) in hexane (4 mL plus 1 mL rinse) and Et_3B (0.76 mL, 1M in hexane, 0.76 mmol) were added simultaneously to a solution of aldehyde **157c** (127.0 mg, 0.348 mmol) in hexane (70 mL) over 20 sec. Air (10 mL) was then bubbled though the solution over 20 sec and stirring, without protection from the atmosphere, was continued for 12 h. At this point the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (1M solution in hexane, 0.76 mL, 0.76 mmol) were added and stirring was continued for 10 h. The reaction mixture was evaporated and flash chromatography of the crude product over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave the isomeric alcohols **197** and **198**, which were not characterized, but directly oxidized to ketone **166c**, as described in the following experiment.

Methyl (4aα, 8aβ)-1,2,3,4,4a,5,8,8a-octahydro-3-oxonaphthalene-4a-carboxylate (166c).



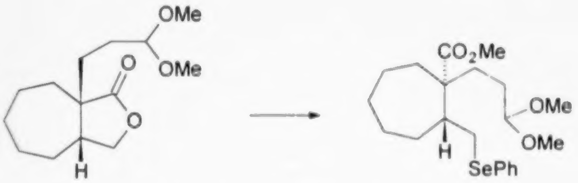
PCC (224.0 mg, 1.04 mmol) and powdered 4 Å molecular sieves (50 mg) were added to a solution of alcohols **197** and **198** in CH_2Cl_2 (10 mL). The resulting mixture was stirred under argon for 5 h and then filtered through Celite (3 x 10) cm. The pad was washed with CH_2Cl_2 (15 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (3 x 24 cm), using 10% EtOAc-hexane, gave **166c** (51.4 mg, 71% from **157c**) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 1717, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56-1.69 (m, 1 H), 1.87-2.09 (m, 3 H), 2.22-2.40 (m, 5 H), 2.62-2.71 (m, 1 H), 2.83-2.94 (m, 1 H), 2.92 (s, 3 H), 5.57-5.70 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 30.67 (t'), 36.43 (t'), 36.55 (t'), 38.95, (t'), 40.12 (d'), 44.55 (s'), 44.72 (t'), 51.74 (q'), 124,21 (d'), 126.74 (d'), 174.22 (s'), 210.38 (s'); exact mass, *m/z* calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1097. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.40; H, 7.93.

cis-8a-(3,3-Dimethoxypropyl)octahydro-1*H*-cyclohepta[c]furan-1-one (155d).



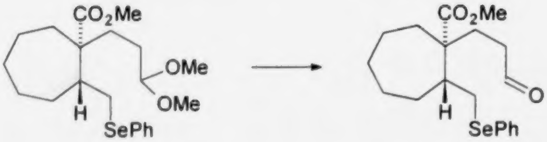
LDA was prepared by rapid additon (*ca.* 60 sec) of *n*-BuLi (6.50 mL, 1.6M solution in hexane, 10.4 mmol) to a magnetically stirred and cooled (ice-bath) solution of *i*-Pr_2NH (1.46 mL, 10.4 mmol) in THF (40 mL). The solution was then cooled to -78 °C and, after an additional 30 min, a solution of lactone **154d** (1.4656 g, 9.50 mmol) in THF (10 mL plus 3 mL as a rinse) was added by cannula over 2 min. The resulting solution was stirred for 30 min and then *n*-BuLi (1.00 mL, 1.60 mmol) was added and stirring wascontinued for 10 min at -78°C, at which point freshly prepared iodide **153** (2.90 g, 12.6 mmol) was added neat in one portion. The cold bath was removed and stirring was continued for 24 h. Cold saturated aqueous NH_4Cl (5 mL) was added and the solution was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (4 x 25 cm), using EtOAc-hexane mixtures (6 to 15% EtOAc), gave acetal **155d** (1.8938 g, 77%) as a pure [^1H NMR (200 MHz)], oil: FT-IR ($CHCl_3$ cast) 2927, 2856, 1762, 1191 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHZ) δ 1.30-1.46 (m, 2 H), 1.30-1.74 (br m, 11 H), 1.74-1.82 (m, 1 H), 2.27-2.35 (m, 1 H), 3.23 (s, 3 H), 3.26 (s, 3 H), 3.83-3.88 (dd, *J* = 10, 4 Hz, 1 H), 4.25 (t, *J* = 5Hz, 1 H), 4.32 (t, *J* = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.96 (t'), 27.21 (t'), 27.28 (t'), 30.70 (t'), 31.81 (t'), 35.15 (t', I assume two signals are coincident), 44.78 (d'), 49.38 (s'), 52.70 (q'), 53.02 (q'), 71.38 (t'), 104.25 (d'), 181.66 (s'); exact mass, *m/z* calcd for $C_{14}H_{24}O_4$ $[(M-H)]^+$ 255.1592, found 255.1596. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.34; H, 9.00.

Methyl *cis*-1-(3,3-dimethoxypropyl)-2-[(phenylseleno)methyl]cycloheptanecarboxylate (156d).



A literature procedure[35] for cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (12 mL) was added to a mixture of PhSeSePh (1.0175 g, 4.34 mmol) and NaH (234.4 mg, 60% dispersion in oil, 5.46 mmol) and the resulting slurry was refluxed for 50 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry, degassed HMPA (1.0 mL) was added. The precipitate dissolved, and a solution of lactone **155d** (1.1112 g, 4.34 mmol) in THF (6 mL plus 2 mL as a rinse) was added by cannula, and the mixture was refluxed for 48 h. It was then cooled to room temperature, quenched with MeOH (4 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 12 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine, dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **156d**. Evaporation of the solvent and lash chromatography of the crude product over silica gel (5 x 23 cm), using EtOAc-hexane mixtures (7 to 15% EtOAc), gave **156d** (929.6 mg, 50%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (200 MHz)], yellow oil: FT-IR ($CHCl_3$ cast) 2926, 1724, 1437, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22-2.09 (br m, 15 H), 2.65 (t, J = 12 Hz, 1 H), 3.00-3.10 (m, 1 H), 3.31 (s, 6 H), 3.65 (s, 3 H), 4.30 (t, J = 4.5 Hz, 1 H), 7.20-7.36 (m, 3 H), 7.45-7.60 (m, 2H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 22.02 (t'), 27.03 (t'), 27.50 (t'), 27.72 (t'), 29.03 (t'), 30.98 (t'), 31.70 (t'), 32.10 (t'), 47.19 (d'), 51.36 (q'), 52.23 (q'), 52.75 (q'), 52.79 (s'), 104.53 (d'), 126.91 (d'), 128.90 (d'), 130.30 (s'), 133.13 (d'), 176.40 (q'); exact mass, *m/z* calcd for $C_{21}H_{32}O_4Se$ 428.1465, found 428.1454. Anal. Calcd for $C_{21}H_{32}O_4Se$: C, 59.01; H, 7.55; O, 14.97. Found: C, 59.13; H, 7.82; O, 14.76.

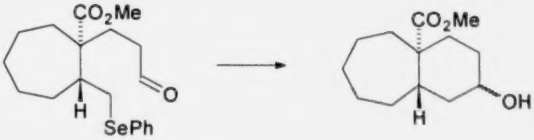
Methyl *cis*-1-(3-oxopropyl)-2-[(phenylseleno)methyl]cycloheptanecarboxylate (157d).



A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 30 mL) was added to a solution of acetal **156d** (679.7 mg, 1.59 mmol) in $CHCl_3$ (50 mL) and the resulting heterogeneous mixture was stirred vigorously for 18 h at room temperature. The mixture was then cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 10 mL), brine (1 x 10 mL), dried, and concentrated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (10 to 20% EtOAc), gave aldehyde **157d** (594.2 mg, 94%) as a pure [^{1}H NMR (200 MHz)], oil: FT-IR ($CHCl_3$ cast) 2924, 1722, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17-1.52 (br m, 3 H), 1.53-2.15 (br m, 10 H), 2.26-2.92 (m, 2 H), 2.53 (br t, J = 12 Hz, 1 H), 3.05 (dd, J = 12, 2.5 Hz, 1 H), 3.64 (s, 3 H), 7.20-7.37 (m, 3 H), 7.49-7.60 (m, 2 H), 9.76 (t, J = 1.5 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 75.496 MHz) δ 22.02 (t'), 27.61 (t'), 27.71 (t'), 27.85, (t') 29.08 (t'), 31.76 (t'), 32.42 (t'), 39.44 (t'), 47.23 (d'), 51.24 (d'), 52.30 (s'), 126.99 (d'), 128.62 (d'), 129.89 (s'), 133.35 (d'), 175.68 (s'), 200.98

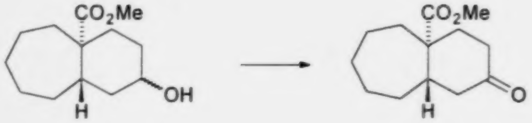
(d'); exact mass, *m/z* calcd for $C_{19}H_{26}O_3Se$ 382.1047, found 382.1045. Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.84; H, 6.87; O, 12.59. Found: C, 60.10; H, 6.58; O, 12.35.

Methyl (4aα, 9aβ)-decahydro-2α-hydroxy-4a*H*-cyclohexacycloheptan-4a-carboxylate (199) and Methyl (4aα, 9aβ)-decahydro-2β-hydroxy-4a*H*-cyclohexacycloheptan-4a-carboxylate (200).



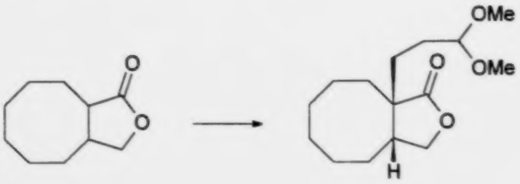
Ph_3SnH (540.0 mg, 1.54 mmol) and Et_3B (2.60 mL, 1M in hexane, 2.60 mmol) in hexane (8 mL plus 3 mL as a rinse) were added simultaneously over 30 sec to a stirred solution of **157d** (451.0 mg, 1.18 mmol) in hexane (100 mL). Air (20 mL) was then bubbled though the solution over 30 sec, and stirring, without protection from the atmosphere, was continued for 8 h. At this point, the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (1.00 mL, 1M in hexane, 1.00 mmol) were added and stirring was continued for 15 h. The solution was evaporated and flash chromatography of the crude product over silica gel (3 x 23 cm), using 8% EtOAc-hexane, gave the isomeric alcohols **199** and **200**. These were not characterized, but used directly in the next experiment.

Methyl (4aα, 9aβ)-decahydro-2-oxo-4a*H*-cyclohexacyclohepta-4a-carboxylate (166d).



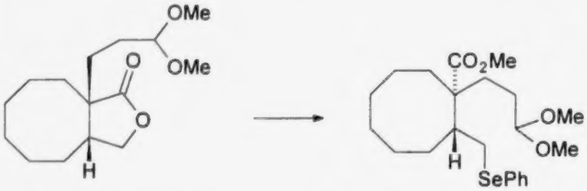
PCC (778.7 mg, 3.54 mmol) and powdered 4 Å molecular sieves (200 mg) were added to a solution of alcohols **199** and **200** CH_2Cl_2 (20 mL). The resulting solution was stirred under argon for 7 h and then filtered through Celite (3 x 10) cm. The pad was washed with CH_2Cl_2 (25 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (3 x 19 cm), using 8% EtOAc-hexane, gave ketone **166d** (211.8 mg, 80%) as a pure [^{1}H NMR (400 MHz)], clear oil: FT-IR ($CDCl_3$ cast) 2927, 2862, 1718, 1460, 1431 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.75 (br m, 10 H), 1.83-2.09 (m, 2 H), 2.15-2.31 (m, 4 H), 2.79-2.88 (m, 1 H), 3.73 (s, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.31 (t'), 26.33 (t'), 26.51 (t'), 33.27 (t'), 38.32 (t'), 38.35 (t'), 38.48 (t'), 46.49 (t'), 47.19 (d'), 49.42 (s'), 51.49 (q'), 175.56 (s'), 211.18 (s'); exact mass, *m/z* calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1411. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 8.99. Found: C, 69.68; H, 8.99.

***cis*-9a-(3,3-Dimethoxypropyl)octahydrocycloocta[c]furan-1(3*H*)-one (155e).**



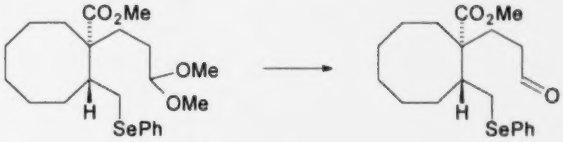
LDA was prepared by rapid additon (*ca.* 60 sec) of *n*-BuLi (6.90 mL, 1.6M in hexane, 11.0 mmol) to a magnetically stirred and cooled (ice-bath) solution of *i*-Pr_2NH (1.54 mL, 11.0 mmol) in THF (40 mL). The solution was then cooled to -78°C and, after an additional 10 min, a solution of lactone **154e** (1.6797 g, 9.98 mmol) in THF (10 mL plus 3 mL as a rinse) was added by cannula over 1 min. The resulting solution was stirred for 30 min and then *n*-BuLi (2.00 mL, 1.6M in hexane, 3.2 mmol) was added. The solution was stirred for 10 min at -78°C at which point freshly prepared iodide **153** (3.00 g, 13.04 mmol) was added neat in one portion. The cold bath was removed and stirring was continued for 19 h. The reaction was quenched with cold saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 20 mL). The combined ethereal extracts were washed with brine (1 x 10 mL), dried , and evaporated. Flash chromatography of the crude product over silica gel gave **155e** (1.6955 g, 63%) which contained traces [^{1}H NMR (200 MHz)] of an impurity, amounting to <3% on the basis that it is the tranbs isoemr. The material had: FT-IR ($CHCl_3$ cast) 2928, 2856, 1763, 1467, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHZ) δ 1.06-1.51 (m, 3 H), 1.52-1.96 (br m, 13 H), 2.05-2.13 (m, 1 H), 3.25 (s, 3 H), 3.28 (s, 3 H), 3.84 (d, $J = 9$ Hz, 1 H), 4.21-4.29 (m, 1 H), 4.45 (dd, $J = 10, 8$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.33 (t'), 24.24 (t'), 24.86 (t'), 25.59 (t'), 26.99 (t'), 27.94 (t'), 30.74 (t'), 32.45 (t'), 47.21 (d'), 47.95 (s'), 52.92 (q'), 52.98 (q'), 75.07 (t'), 104.36 (d'), 180.53 (s'); exact mass, *m/z* calcd for $C_{15}H_{26}O_4$ [(M-H)]$^+$ 269.1753, found 269.1766. An analytical sample was obtained by recrystallization from hexane: 58-59 °C. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.42; H, 9.54.

Methyl *cis*-1-(3,3-dimethoxypropyl)-2-[(phenylseleno)methyl]cyclooctanecarboxylate (156e).



A literature procedure[35] for cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (10 mL) was added to a mixture of PhSeSePh (658.6 mg, 2.11 mmol) and NaH (151.6 mg, 60% dispersion in oil, 3.79 mmol) and the resulting slurry was refluxed for 60 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry, degassed HMPA (0.5 mL) was added. The precipitate dissolved, and a solution of lactone **155e** (760.9 mg, 2.81 mmol) in THF (8 mL plus 2 mL as a rinse) was added by cannula, and the mixture was refluxed for 24 h. It was then cooled to room temperature, quenched with MeOHl (4 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (1 x 10mL), dried, and evaporated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **156e**. Flash chromatography of the crude product over silica gel (4 x 20 cm), using 10% EtOAc-hexane, gave unreacted lactone **155e** [^{1}H NMR, (400 MHz)] (198.6 mg, 26%) and selenide **156e** (557.9 mg, 45%, 61% based on recovered starting material) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR, (400 MHz)], yellow oil: FT-IR ($CHCl_3$ cast) 2924, 1723, 1476, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12-1.70 (br m, 13 H), 1.70-1.82 (m, 2 H), 1.90-2.03 (m, 2 H), 3.30 (s, 3 H), 3.31 (s, 3 H), 3.63 (s, 3 H), 4.31 (t, $J = 6$ Hz, 1 H), 7.20-7.28 (m, 3 H), 7.48-7.52 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.98 (t'), 25.93 (t'), 26.89 (t'), 27.51 (t'), 28.15 (t'), 29.00 (t'), 30.16 (t'), 30.31 (t'), 33.96 (t'), 44.88 (d'), 51.32 (q'), 52.13 (s'), 52.22 (q'), 53.06 (q'), 104.78 (d'), 126.94 (d'), 128.98 (d'), 130.31 (s'), 135.15 (d'), 175.62 (s'); exact mass, *m/z* calcd for $C_{22}H_{34}O_4Se$ 442.1622, found 442.1610. Anal. Calcd for $C_{22}H_{34}O_4Se$: C, 59.85; H, 7.76. Found: C, 59.74; H, 7.85.

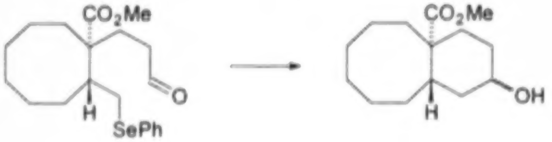
Methyl *cis*-1-(3-oxopropyl)-2-[(phenylseleno)methyl]cyclooctanecarboxylate (157e).



A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 25 mL) was added to a solution of acetal **156e** (550.0 mg, 0.25 mmol) in $CHCl_3$ (40 mL) and the resulting heterogeneous mixture was stirred vigorously for 10 h at room temperature. The resulting mixture was cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (3 x 18 cm), using 10% EtOAc-hexane, gave aldehyde **157e** as a pure [^{1}H NMR, (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2919, 1722, 1476, 1436, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15-1.82 (br m, 12 H), 1.93-2.05 (m, 1 H), 2.18-2.35 (m, 4 H), 2.38-2.49 (m, 1 H), 3.25 (dd, $J = 12, 1.5$ Hz, 1 H), 3.62 (s, 3 H), 7.29-7.30 (m, 3 H), 7.42-7.53 (m, 2 H), 9.69 (t, $J = 1.5$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.06 (t'), 25.87 (t'), 26.51 (t'), 27.47 (t'), 30.08 (t'), 30.32 (t'), 33.83 (t'), 39.87 (t'), 44.96 (d'), 51.36 (q'), 51.59 (s'), 127.12 (d'), 128.99 (d'), 129.85

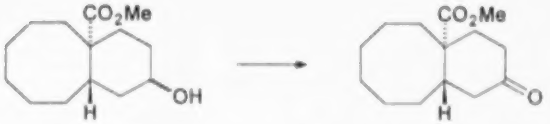
(s'), 133.34 (d'),175.15 (s'), 201.55 (d', we assume that two signals are coincident); exact mass, *m/z* calcd for $C_{20}H_{28}O_3Se$ 396.1203, found 396.1208. Anal. Calcd for $C_{20}H_{28}O_3Se$: C, 60.75; H, 7.14. Found: C, 60.88; H, 7.10.

Methyl (4aα, 10aβ)-dodecahydro-2α-hydroxy-4a*H*-cyclohexacyclooctane-4a-carboxylate (201) and Methyl (4aα, 10aβ)-dodecahydro-2β-hydroxy-4a*H*-cyclohexacyclooctane-4a-carboxylate (202).



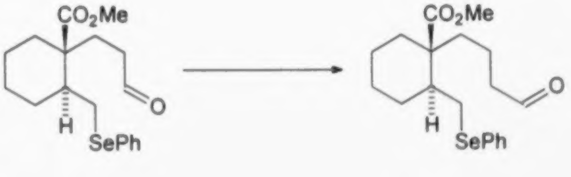
Ph_3SnH in hexane (6 mL plus 2 mL rinse) and Et_3B (1.0 mL, 1M in hexane, 1.0 mmol) were added simultaneously over 15 sec to a stirred solution of aldehyde **157e** (144.1 mg, 0.401 mmol) in hexane (50 mL). Air (20 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued. After the material had been stirred for 6 h at room temperature, open to the atmosphere, the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (0.76 mL, 1M in hexane, 0.76 mmol) were added and stirring was continued for 12 h. The mixture was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave the isomeric alcohols **201** and **202**, which were not characterized, but oxidized directly to ketone **166e**, as described in the following experiment.

Methyl (4aα, 10aβ)-Dodecahydro-2-oxo-4a*H*-cyclooctan-4a-carboxylate (166e)



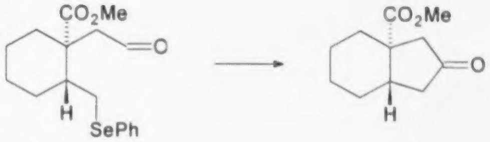
PCC (290.0 mg, 1.33 mmol) and powdered 4 Å molecular sieves (120 mg) were added to a solution of the above alcohols **201** and **202** CH_2Cl_2 (20 mL) The resulting solution was stirred under argon for 9 h and filtered through Celite (3 x 10) cm. The pad was washed with CH_2Cl_2 (20 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 8% EtOAc-hexane, gave ketone **166e** (819.0 mg, 77%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2923, 1719, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.32 (br m, 11 H), 1.93-2.20 (m, 5 H), 2.21-2.31 (m, 1 H), 2.39 (dt, *J* = 15, 6.0 Hz, 1 H), 2.66 (t, *J* = 14 Hz, 1 H), 3.70 (s, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.46 (t'), 25.40 (t'), 26.45 (t'), 28.61 (t'), 32.50 (t'), 35.39 (t'), 35.53 (t'), 38.57 (t'), 39.56 (d'), 46.83 (t'), 49.40 (s'), 51.47 (q'), 175.84 (s'), 211.23 (s'); exact mass, *m/z* calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1570. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.27; H, 9.59.

Methyl *cis*-1-(4-oxobutyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (167).



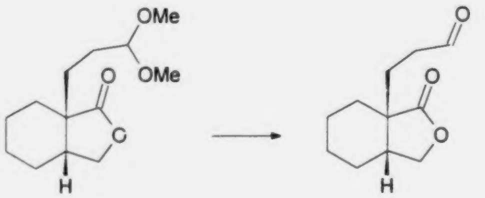
n-BuLi (0.56 mL, 1.6M, 0.898 mmol) was added to a stirred and cold (-78°C) and stirred solution of (methoxymethyl)triphenylphosphonium chloride[51] (307.9 mg, 0.898 mmol) in THF (10 mL) over 30 s. The resulting orange solution was stirred for 30 min at 20°C and then added by cannula (using THF 5mL as a rinse) to a stirred solution (20°C) of aldehyde **157b** (165.0 mg, 0.449 mmol) in THF (10 mL). The resulting solution was stirred for 8 h, poured into water (100 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The organic extract was dried and evaporated. The resulting oil was dissolved in *p*-dioxane (11 mL) and water (7 mL) and *p*-toluenesulfonic acid (20 mg) were added. The mixture was stirredat room temperature for 12 h and then refluxed for 15 h. The mixture was then cooled, and extracted with EtOAc (3 x 15 mL). The organic extracts were washed with brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (7 to 15% EtOAc), gave **167** (119.6 mg, 70%) as a pure [^{1}H NMR, (400MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 2942, 2935, 2931, 2860, 1722, 1477, 1448, 1436, 1285 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15-2.00 (br m, 13 H), 2.25-2.40 (m, 2 H), 2.83-3.10 (m, 2 H), 3.59 (s, 3 H), 7.15-7.30 (m, 3 H), 7.41-7.55 (m, 2 H), 9.68 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 50 MHz) δ 16.77 (t'), 22.32 (t'), 23.25 (t'), 26.51 (t'), 29.85 (t'), 30.33 (t'), 36.06 (t'), 44.00 (t'), 44.08 (d'), 50.55 (s'), 51.36 (q'), 127.00 (d'), 129.02 (d'), 130.79 (s'), 133.21 (d'), 176.25 (s'), 201.68(d'); exact mass, *m/z* calcd for $C_{19}H_{26}O_3Se$ 382.1049, found 382.1050. Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.83; H, 6.87. Found: C, 59.77 H, 6.72.

Methyl *trans*-octahydro-2-oxo-3a*H*-indene-3a-carboxylate (171).



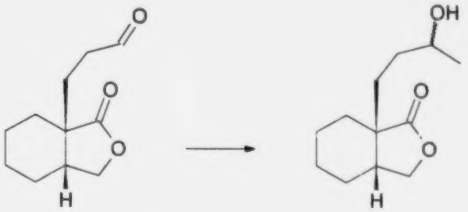
Ph_3SnH (206 mg, 0.586 mmol) in hexane (7 mL plus 2 mL rinse) and Et_3B (0.90 mL, 1M in hexane 0.9 mmol) were added simultaneously over 40 sec to a solution of aldehyde **170** (138 mg, 0.391 mmol) in hexane (90 mL. Air (20 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued for 7 h. At this point the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL rinse) and Et_3B (1 M solution in hexane, 1.0 mL, 1.0 mmol) were added, and stirring was continued for 12 h. The solution was evaporated and flash chomatograpy of the crude product over silica gel (2 x 20 cm), using 10% EtOAc-hexane gave a mixture of isomeric alcohols which were oxidized directly as follows: PCC (150 mg, 0.696 mmol) and powdered 4Å molecular sieves (50 mg) were added in one portion to a stirred solution of the above alcohols in CH_2Cl_2 (15 mL) and the resulting mixture was stirred vigorously at room temperature for 12 h. The mixture was then filtered though a pad of Celite (2 x 10 cm), using CH_2Cl_2 (60 mL) as eluent, and the dark brown filtrate was evaporated. Flash chromatography of the crude product over silica gel (2 x 24 cm), using 5% EtOAc-hexane, gave ketone **171** as a pure [^{1}H NMR, (200 MHz)], oil whose spectral proerties ^{1}H NMR (200 MHz), ^{13}C NMR APT (50 MHz) matched those of an authentic sample prepared by a different route.[34] Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.63; H, 8.26.

***cis*-7a-(3-Oxopropyl)hexahydro-1(3*H*)-isobenzofuranone (172).**



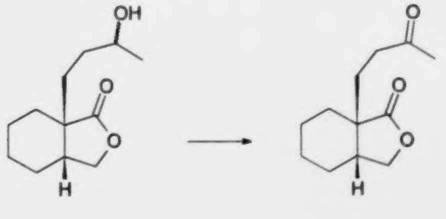
A literature procedure[49] for cleavage of dimethyl acetals was followed with minor modifications: An aqueous solution of TFA (50%, 20 mL) was added to a stirred solution of the acetal **155b** (917.6 mg, 3.79 mmol) in $CHCl_3$ (40 mL) and the resulting heterogeneous mixture was stirred vigorously for 16 h at room temperature. The resulting mixture was cooled in an ice bath and **carefully** titrated (stirring) with saturated aqueous $NaHCO_3$ solution until gas evolution ceased. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 35 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (4 x 18 cm), using EtOAc-hexane mixtures (15 to 30%), gave **172** (623.8 mg, 84%) as a homogeneous [^{1}H NMR, (400 MHz)], yellow oil: FT-IR ($CDCl_3$ cast) 2933, 2859, 1764, 1722, 1112, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23-1.49 (m, 4 H), 1.49-1.52 (m, 2 H), 1.64-1.72 (m, 3 H), 1.93-2.01 (m, 1 H), 2.16-2.20 (m, 1 H), 2.45-2.55 (dt, J = 7.5, 1 Hz, 2 H), 3.88-3.95 (dd, J = 9, 6.5 Hz, 1 H), 4.22-4.28 (dt, J = 9, 6.5 Hz, 1 H), 9.71 (t, J = 9.71 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.51 (t'), 21.87 (t'), 24.97 (t'), 26.03 (t'), 29.02 (t'), 38.50 (t'), 39.1 (d'), 43.99 (s'), 69.20 (t'), 179.87 (s'), 200.92 (d'); exact mass, *m/z* calcd for $C_{11}H_{16}O_3$ [(M + H)$^+$] 197.1174, found 197.1179. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.27.

cis-7a-(3-Hydroxybutyl)hexahydro-1(3*H*)-isobenzofuranone (205).



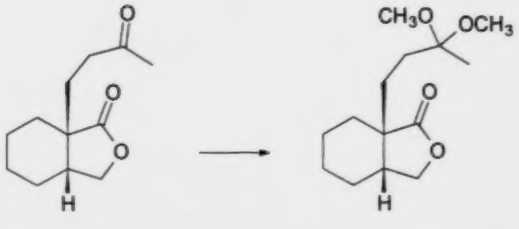
MeLi (1.51 mL, 1.4 M THF solution, 2.12 mmol) was added over 3 min to a stirred and cooled (-50°C) solution of aldehyde **172** (378.5 mg, 1.93 mmol) in THF (10 mL). The cold bath was removed and the solution was allowed to attain room temperature (3 h), and then the mixture was quenched with saturated aqueous NH_4Cl (3 mL), extracted with Et_2O (3 x 30 mL). The combined ethereal extracts were washed with brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (20 to 50% EtOAc), gave recovered **172** (42.6 mg, 11%) as a pure [^{1}H NMR (400 MHz)], homogeneous oil and **205** (249.2 mg, 61%, 69% based on recovered **172**) as a mixture [^{1}H NMR (400 MHz)], of inseparable isomers: FT-IR ($CDCl_3$ cast) 3150-3660 (br), 2930, 2859, 1765, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3 H), 1.18 (s, 3 H), 1.22-1.95 (br m, 13 H), 2.20-2.40 (m, 1 H), 3.63-3.80 (m, 1 H), 3.86-4.00 (m, 1 H), 4.20-4.56 (m, 1 H); exact mass, *m/z* calcd for $C_{12}H_{20}O_3$ [$(M-H)^+$] 211.1333, found 211.1334. The alcohols were characterized by oxidation to ketone **173**.

cis-7a-(3-Oxobutyl)hexahydro-1(3*H*)-isobenzofuranone (173).



PCC (1.20 g, 5.44 mmol) and powdered 4Å molecular sieves (300 mg) were added in one portion to a stirred solution of acohols **205** (231.1 mg, 1.09 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was stirred vigorously at room temperature for 12 h. At this point TLC (silica, 30% EtOAc-hexane) showed some starting material remaining. More PCC (100 mg) was added and stirring was continued for 1 h. The reaction mixture was then filtered through a pad of Celite (2 x 10 cm), using CH_2Cl_2 (100 mL) as eluent, and the dark brown filtrate evaporated. Flash chromatography of the crude product over silica gel (2 x 30 cm), using EtOAc-hexane mixtures (20 to 50% EtOAc), gave ketone **173** as a pure [^{1}H NMR (400 MHz)], oil: FT-IR ($CDCl_3$ cast) 2932, 2859, 1765, 1716 cm^{-1}; ^{1}H NMR δ 1.20-1.33 (m, 4 H), 1.40-1.50 (m, 2 H), 1.64-1.85 (m, 3 H), 1.90-1.99 (m, 1 H), 2.08 (s, 3 H), 2.10-2.14 (m, 1 H), 2.46 (t, *J* = 7.5 Hz, 1 H), 3.89 (dd, *J* = 9, 6 Hz, 1 H), 4.25 (dd, *J* =9, 6 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.67 (t'), 22.07 (t'), 25.38 (t'), 27.92 (t'), 29.15 (t'), 29.85 (d'), 37.80 (t'), 39.44 (q'), 44.14 (s'), 69.40 (t'), 179.98 (s'), 207.48 (s'); exact mass, *m/z* calcd for $C_{12}H_{18}O_3$ 210.1255, found 210.1256. Anal. Calcd for $C_{12}H_{18}O_3$: C, 69.54; H, 8.63. Found: C, 69.62; H, 8.72.

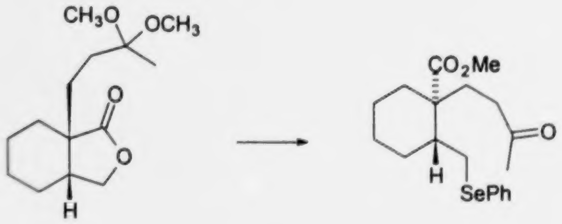
***cis*-7a-(3,3-Dimethoxybutanyl)hexahydro-1(3*H*)-isobenzofuranone (174).**



A solution of ketone **173** (881.2 mg, 11.19 mmol), $(MeO)_3CH$ (35 mL), and *p*-toluenesulfonic acid (10 mg) in dry MeOH (20 mL) was stirred under argon at room temperature for 12 h. The solution was evaporated and the residue was diluted with

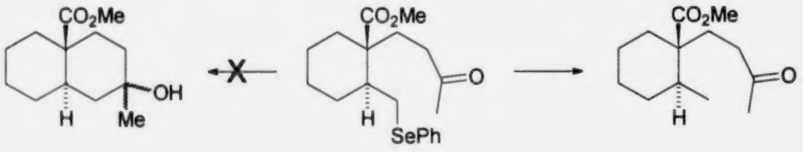
Et_2O (100 mL). The resulting ethereal solution washed with saturated aqueous $NaHCO_3$ (1 x 30 mL). The aqueous layer was extracted with Et_2O (1 x 30 mL) and the combined etheral extracts were washed with brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (3 x 30 cm), using EtOAc-Et_3N-hexane mixtures (15% EtOAc-1% triethylamine to 40% EtOAc), gave recovered **173** (101.0 mg, 11.5%) as a pure [^1H NMR (400 MHz)], oil and **174** (887.7 mg, 83%, 93% based on recovered ketone **173**) as a pure [^1H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2936, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 3 H), 1.20-1.80 (m, 12 H), 2.15-2.24 (m, 1 H), 3.04 (s, 3 H), 3.05 (s, 3 H), 3.89-3.90 (m, 1 H), 4.18-4.22 (m, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 20.62, 21.66, 21.90, 25.14, 28.65, 29.18, 30.50, 38.43, 44.42, 47.78, 69.06, 101.16, 180.13; exact mass, *m/z* calcd for $C_{13}H_{21}O_3$ [$(M - OCH_3)^+$] 225.1484, found 225.1492. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.58; H, 9.73.

Methyl *cis*-1-(3-oxobutyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (175).



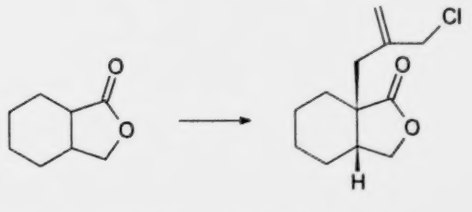
A literature procedure[35] for the cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (8 mL) was added to a mixture of PhSeSePh (265.3 mg, 0.85 mmol) and NaH (61.2 mg, 60% dispersion in oil, 0.53 mmol) and the resulting slurry was refluxed for 50 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature and dry, degassed HMPA (1.0 mL) was added. The precipitate dissolved, and a solution of ketal **174** (289.4 mg, 1.13 mmol) in THF (4 mL plus 3 mL as a rinse) was added via cannula, and the mixture was refluxed for 18 h. The mixture was cooled to room temperature, quenched with MeOH (3 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 8 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **175**. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using EtOAc-hexane mixtures (20 to 30% EtOAc), gave recovered ketone **173** (160.4 mg, 69%) as a pure [^{1}H NMR (400 MHz)], oil and selenide **175** (91.4 mg, 21%, 65% based on recovered **173**) as a pure [^{1}H NMR (400 MHz)], oil: FT-IR ($CDCl_3$ cast) 2936, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.49 (m, 2 H), 1.48-1.63 (m, 4H), 1.70-1.80 (m, 1 H), 1.84-2.02 (m, 4 H), 2.11 (s, 3 H), 2.14-2.33 (m, 2 H), 2.95 (t, J = 13 Hz, 1 H), 3.08 (dd, J = 13, 2 Hz, 1 H), 3.65 (s, 1 H), 7.23-7.32 (m, 3 H), 7.50-7.55 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.10 (t'), 22.98 (d'), 26.15 (t'), 29.69 (t'), 29.97 (q'), 30.13 (t'), 38.12 (t'), 43.80 (d'), 49.60 (t'), 51.40 (q'), 176.05 (s'), 207.69 (s'); exact mass, *m/z* calcd for $C_{19}H_{26}O_3Se$ 382.1035, found 382.1054. Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.84; H, 6.87. Found: C, 59.79; H, 6.86.

Methyl *cis*-1-(3-oxobutyl)-2-methylcyclohexanecarboxylate (176).



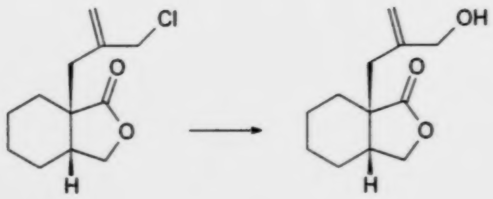
Ph_3SnH (126 mg, 0.359 mmol) and Et_3B (0.53 mL, 1.0 M hexane solution, 0.526 mmol) were added simultaneously, each in one portion, to a solution of the selenide **175** (91.0 mg, 0.239 mmol) in hexane (45 mL) ans stirring, without protection from the atmpshere, At this time the reaction was still incomplete (TLC silica, 30% EtOAc-hexane). Ph_3SnH (50 mg, 0.14 mmol) and Et_3B (0.50 mL, 1.0 M hexane solution, 0.50 mmol) were added and the resulting mixture was stirred for an additional 12 h. Evaporation of the solvent and flash chromatography of the crude product over silica gel (1 x 30 cm), using 5% EtOAc-hexane gave recovered selenide **175** (16.1 mg, 18%) as a pure [^1H NMR (400 MHz)], oil and the product of reduction (**176**) (38.8 mg, 72%, 87% based on recovered **175**) as a homogeneous [^1H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2935, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, $J = 7$ Hz, 3 H), 1.10-2.01 (br m, 12 H), 2.1 (s, 3 H), 2.19-2.48 (m, 1 H), 3.64 (s, 3 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 16.52 (q'), 21.87 (t'), 22.37 (t'), 28.07 (s'), 29.42 (t'), 29.77 (t'), 29.93 (q'), 37.59 (q'), 38.91 (t'), 48.66 (t'), 51.17 (q'), 176.72 (s'), 208.23 (s'); exact mass, *m/z* calcd for $C_{13}H_{22}O_3$ 226.1563, found 226.1570. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.69; H, 10.02.

cis-7a-(2-Chloromethyl-2-propenyl)hexahydro-1(3*H*)-isobenzofuranone (181).



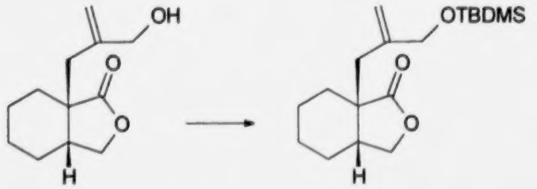
LDA was prepared by addition (*ca* 60 sec) of *n*-BuLi (10.7 mL, 1.6M in hexane, 17.13 mmol) to a magnetically stirred and cooled (ice-bath) solution of *i*-Pr_2NH (2.40 mL, 17.13 mmol) in THF (40 mL). The solution was then cooled to -78 °C and, after an additional 10 min, a solution of lactone **154b** (2.1835 g, 15.58 mmol) in THF (11 mL plus 5 mL as a rinse) was added via cannula over 30 sec. The resulting yellow solution was stirred for 10 min, and then *n*-BuLi (4 mL, 1.6M in hexane, 6.4 mmol) was added in one portion. Stirring was continued for an additional 5 min and then the dichloride **180** (6.0 mL, 51.84 mmol) was added neat in one portion. The cooling bath was left in place and stirring was continued overnight, during which time the mixture attained room temperature and turned an orange color. The mixture was poured into 5% aqueous HCl (30 mL) and extracted with ether (3 x 40 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the crude product over silica gel (4 x 20 cm), using 10% EtOAc-hexane, gave **181** (3.1407 g, 88%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], yellow oil: FT-IR (CH_2Cl_2 cast) 2934, 2860, 1766, 1450, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.53 (m, 6 H), 1.62-1.82 (m, 2 H), 2.37-2.96 (m, 1 H), 2.55 (dd, *J* = 27, 9 Hz, 2 H), 3.95-4.10 (m, 3 H), 4.25 (dd, J = 9, 8 Hz, 1 H), 5.00 (d, J = 1 Hz, 1 H), 5.27, (m, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.29 (t'), 21.41 (t'), 23.86 (t'), 29.89 (t'), 36.72 (t'), 37.49 (d'), 44.64 (s'), 48.58 (t'), 68.72 (t'), 119.63 (t'), 140.63 (s'), 180.51 (s'); exact mass, *m/z* calcd for $C_{12}H_{17}O_2$ $[(M-Cl)]^+$ 193.1229, found 193.12279. Anal. Calcd for $C_{12}H_{17}O_2$: C, 63.01; H, 7.49. Found: C, 63.12; H, 7.63.

cis-6a-(2-Hydroxymethyl-2-propenyl)hexahydro-1(3_H_)-isobenzofuranone (182).



$CaCO_3$ (300 mg) was added to a solution of chloride **181** (121.6 mg, 0.532 mmol) in dioxane (3 mL) and water (3 mL).[56] The resulting mixture was stirred vigorously and refluxed, open to the atmosphere, for 12 h, cooled, acidified with 10% aqueous HCl (20 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried and evaporated. Flash chromatography of the residual oil over silica gel (1 x 19 cm), using EtOAc-hexane mixtures (40 to 50% EtOAc) gave recovered **181** (12.2 mg, 10%) and allylic alcohol **182** (87.7 mg, 78%, 87% based on recovered **181**) as a pure [TLC, silica, 30% EtOAc-hexane, ^1H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 3510-3402 (br), 2931, 2859, 1763, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31-1.73 (br m, 8 H), 2.33-2.61 (m, 4 H), 3.98 (d, $J = 6$ Hz, 2 H), 4.06 (t, $J = 9$ Hz, 1 H), 4.25 (dd, $J = 10, 8$ Hz, 1 H), 4.93 (s, 1 H), 5.11-5.17 (m, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 20.98 (t'), 21.02 (t'), 22.56 (t'), 29.88 (t'), 36.08 (t'), 36.70 (d'), 44.23 (s'), 65.50 (t'), 68.54 (t'), 115.32 (t'), 144.47 (s'), 182.43 (s'); exact mass, *m/z* calcd for $C_{12}H_{18}O_3$ $[(M+H)]^+$ 211.1334, found 211.1336. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.05; H, 8.78.

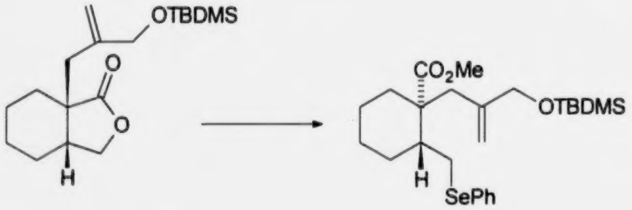
cis-6a-(2-Hydroxy-2[[[[Dimethyl(1,1-dimethylethyl)]silyl]oxy]methyl]-2-propenyl]hexa-hydro-1(3*H*)-isobenzofuranone (183).



t-$BuMe_2SiCl$ (754 mg, 5.00 mmol) and imidazole (340.4 mg, 5.00 mmol) were added to a stirred solution of alcohol **182** (695.4 mg, 3.31 mmol) in THF (30 mL).[57] The mixture was stirred for 5 h , at which point (TLC control silica, 50% EtOAc) showed no starting material remaining. The solution was diluted with Et_2O

(20 mL) and filtered through Celite (3 x 4 cm), using ether (30 mL) as eluent. The filtrate was evaporated, and flash chromatography of the crude product over silica gel (2.5 x 16 cm) with EtOAc-hexane mixtures (3 to 10% EtOAc) gave **183** (744.3 mg, 70%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil which crystallized on standing to a white solid: mp 50 - 52 °C; FT-IR (CH_2Cl_2 cast) 2930, 2857, 1771, 1472, 1252, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 6 H), 0.9 (s, 9 H), 1.49-1.55 (br m, 6 H), 1.60-1.79 (m, 2 H), 2.36-2.55 (m, including a singlet at δ 2.41, 3 H), 3.95-4.10 (m, 3 H), 4.27 (dd, *J* = 9, 7.5 Hz, 1 H), 4.91-4.95 (m, 1 H), 5.26 (dd, *J* = 4.5, 2 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -5.48 (q'), 18.30, (s'), 21.42 (t'), 21.47 (t'), 23.88 (t'), 25.86 (q'), 30.11 (t'), 36.73 (t'), 36.86, (d'), 44.67 (s'), 66.01 (t'), 68.63 (t'), 113.62 (t'), 144.06 (s'), 180.97 (s'); exact mass, *m/z* calcd for $C_{17}H_{29}O_3Si$ [(M - CH_3^+)]$^+$ 309.1886, found 309.1885. Anal. Calcd for $C_{17}H_{29}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.44; H, 10.09.

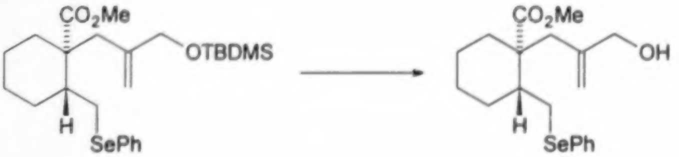
Methyl *cis*-[1-2[[[[dimethyl(1,1-dimethylethyl)]silyl]oxy]methyl]-2-propenyl]-2-[(phenylseleno)methyl]cyclohexanecarboxylate (184).



A literature procedure[35] for cleavage of lactones using phenyl selenide anion was followed with slight modifications: THF (4 mL) was added to a mixture of PhSeSePh (402.6 mg, 1.29 mmol) and NaH (92.8 mg, 60% dispersion in oil, 2.32 mmol) and the resulting slurry refluxed for 50 min, at which point a thick yellow precipitate had appeared. The mixture was cooled to room temperature, and dry

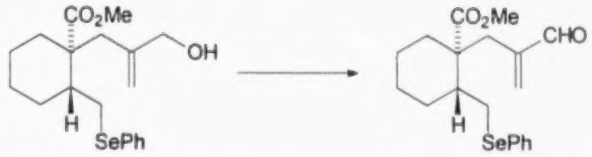
HMPA (0.75 mL) was added. The precipitate dissolved, and a solution of lactone **183** 559.1 mg. 1.72 mmol) in THF (2 mL plus 1 mL as a rinse) was added by cannula. The mixture was refluxed for 30 h, cooled to room temperature, quenched with MeOH (2 mL), acidified (litmus red) by addition of cold (0°C) HCl (0.5M, 6 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried, and concentrated. Titration of the resulting acid with ethereal CH_2N_2 then gave crude ester **184**. Evaporation of the ether and flash chromatography of the crude product over silica gel (2 x 22 cm), using 20% CH_2Cl_2-hexane, gave **183** (82.8 mg, 19%) and selenide **184** (619.6 mg, 73%, 85% based on recovered **183**) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], yellow oil: FT-IR (CH_2Cl_2 cast) 2948, 2929, 2884, 2856, 1729, 1472, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6 H), 0.89 (s, 9 H) 1.25-1.42 (m, 2 H), 1.45-1.61 (m, 4 H), 1.74-1.81 (m, 1 H), 1.83-1.95 (m, 1 H), 2.33 (d, J = 14 Hz, 1 H) 2.49 (d, J = 14 Hz, 1 H), 2.94 (t, J = 11 Hz, 1 H), 3.09 (dd, J = 12.5, 2 Hz, 1 H), 3.88-3.98 (m, 2 H), 4.75 (s, 1 H), 5.12-5.17 (m, 1 H), 7.19-7.29 (m, 3 H), 7.45-7.53 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ -5.38 (q'), 18.33 (t'), 22.11 (t'), 22.66 (s'), 25.68 (q'), 26.25 (t'), 29.46 (s'), 30.08 (t'), 39.34 (t'), 44.69 (d'), 50.53 (t'), 51.18 (q'), 66.24 (t'), 112.84 (t'), 126.81 (d'), 128.97 (d'), 130.75 (s'), 132.76 (d'), 144.36 (s'), 176.25 (s'); exact mass, *m/z* calcd for $C_{25}H_{40}O_3SiSe$ 496.1911, found 496.1919. Anal. Calcd. for $C_{25}H_{40}O_3SiSe$: C, 60.58; H, 8.14. Found: C, 60.43; H, 8.15.

Methyl *cis*-1-[(2-hydroxymethyl)-2-propenyl]-2-[(phenylseleno)methyl]cyclohexanecarboxylate (206).



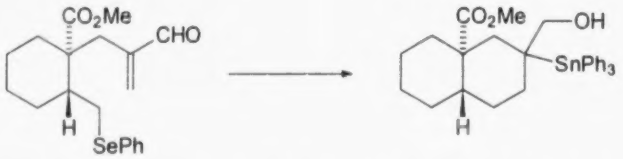
AcOH (8 mL) and water (3 mL) was added to a soluton of silyl ether **184** (248.4 mg, 0.501 mmol) in THF (3 mL).[57] The resulting mixture was stirred at room temperature for 12 hrs, cooled (0°C), and titrated with saturated aqueous $NaHCO_3$ solution until bubbling ceased. The mixture was then extracted with CH_2Cl_2 (4 x 15 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (1 x 10 mL) and the combined organic extracts were dried and evaporated. Flash chromatography of the crude product over silica gel (2 x 16 cm), with EtOAc-hexane mixtures (20 to 35% EtOAc), gave **206** (177.8 mg, 93%) as a homogeneous [TLC, silica, 30% EtOAc-hexane, ^1H NMR (400 MHz)], viscous oil: FT-IR (CH_2Cl_2 cast) 3620-3200 (br), 2941, 2864, 1725, 1578, 1477, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.40 (m, 2 H), 1.14-1.62 (m, 4 H) 1.70-1.95 (m, 3 H), 2.05 (s, 1 H), 2.31 (d, $J = 14$ Hz, 1 H), 2.58 (d, $J = 14$ Hz, 1 H), 2.91 (t, $J = 12$ Hz, 1 H), 3.09 (dd, $J = 13, 3$ Hz, 1 H), 3.62 (s, 3 H), 3.90 (s, 2 H), 4.82 (s, 1 H), 5.13 (q, $J = 1.5$ Hz, 1 H), 7.20-7.31 (m, 3 H), 7.45-7.52 (m, 2 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 21.94 (t'), 22.52 (t'), 26.13, (t'), 29.30 (s'), 29.95 (t'), 39.55 (t'), 44.65 (d'), 50.26 (t'), 51.32 (q'), 65.97 (t'), 114.14 (t'), 126.83 (d'), 128.93 (d'), 130.54 (s'), 132.77 (d'), 144.79 (s'), 176.51 (s'); exact mass, *m/z* calcd for $C_{19}H_{26}O_3Se$ 382.1047, found 382.1051. Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.84; H, 6.87. Found: C, 59.89; H, 6.96.

Methyl *cis*-1-(2-methylene-3-oxopropyl)-2-[(phenylseleno)methyl]cyclohexanecarboxylate (185).



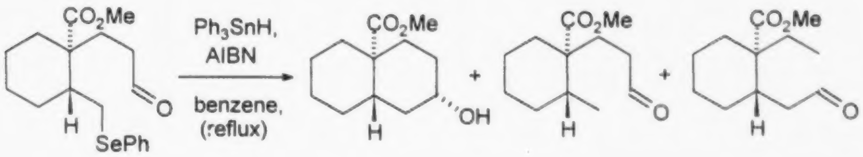
Ph_3BiCO_3[58] (460 mg, 0.917 mmol) was added to a solution of alcohol **206** (177.8 mg, 0.466 mmol) in CH_2Cl_2 (15 mL). The mixture was refluxed under argon for 12 h, cooled, filtered through a mixture (5:1) of Celite:$MgSO_4$ using CH_2Cl_2 (15 mL) as eluent. The filtrate was evaporated and flash chromatography of the crude product over silica gel (2 x 18 cm), using 7% EtOAc-hexane, gave **185** (171.8 mg, 97%) as a pure [^{1}H NMR (400 MHz)], pale orange oil: FT-IR (CH_2Cl_2 cast) 2936, 2861, 1727, 1693, 1437, 1282 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10-1.19 (m, 1 H), 1.26-1.38 (m, 1 H), 1.40-1.62 (br m, 4 H), 1.73-1.83 (m, 2 H), 1.90-2.00 (m, 1 H), 2.53 (d, J = 13 Hz, 1 H), 2.73 (d, J = 13 Hz, 1 H), 2.93-3.03 (m, 1 H), 3.27 (dd, J = 13, 2 Hz, 1 H), 3.59 (s, 3 H), 6.08, (s, 1 H), 6.15 (s, 1 H), 7.20-7.29 (m, 3 H), 7.48-7.54 (m, 2 H), 9.45 (s, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 22.04 (t'), 22.97 (s'), 26.56, (t'), 30.20 (t'), 33.39 (t'), 44.68 (d'), 50.86 (t'), 51.29 (q'), 126.87 (d'), 128.97 (d'), 130.63 (s'), 132.87 (d'), 146.11 (s'), 175.25 (s'), 193.96 (d'); exact mass, *m/z* calcd for $C_{19}H_{24}O_3Se$ 380.0891, found 380.0905. Anal. Calcd for $C_{19}H_{24}O_3Se$: C, 60.15; H, 6.38. Found: C, 60.26; H, 6.41.

Methyl *trans*-3-hydroxymethyl-3-triphenylstannyl-(4aβ, 8aα)-Decahydronaphthalene-4a-carboxylate (186).



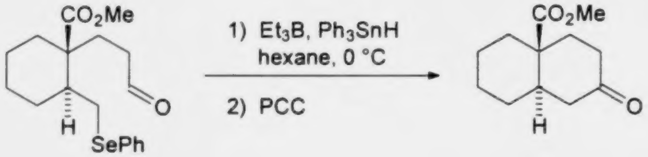
Ph_3SnH (51.6 mg, 0.148 mmol) in hexane (2 mL plus 1 mL rinse) and Et_3B (0.5 mL, 1M solution in hexane, 0.5 mmol) were added simultaneously over 15 sec to a solution of aldehyde **185** (27.9 mg, 0.074 mmol) in hexane (20 mL). Air (10 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued for 8 h. Evaporation of the solvent and flash chromatography of the crude product over silica gel (2 x 18 cm), using 7% EtOAc-hexane, gave **186** (13.9 mg,33%) as a pure [^{1}H NMR (400 MHz)], waxy solid: FT-IR (CH_2Cl_2 cast) 3569, 3555, 3507. 3480. 2987, 1727, 1428, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01-1.22 (m, 3 H), 1.28-1.82 (br m, 10 H), 1.83-2.04 (m, 2 H), 3.27-3.49 (m, 2 H, simplifies to a quartet when D_2O is added), 3.65 (s, 3 H), 7.29-7.39 (m, 9 H), 7.48-7.63 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.40 (t'), 25.61 (t'), 25.99, (t'), 26.15 (t'), 37.21 (t'), 42.21 (t'), 44.97 (t'), 48.93 (d'), 51.20 (d'), 51.30 (t'), 53.31 (t'), 72.37 (t'), 128.09 (d'), 128.33 (d'), 128.49 (d'), 128.55 (d'), 136.78 (d'), 136.96 (d'), 137.14 (d'), 141.21 (s'), 176.91 (s'); exact mass, *m/z* calcd for $C_{25}H_{31}O_3Sn$ [(M - $C_6H_5^+$)]$^+$ 499.1295, found 499.1306.

Thermal Radical Cyclization



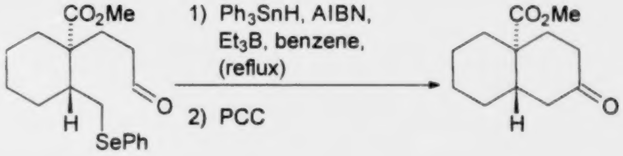
A benzene (10 mL) solution of Ph3SnH (197.7 mg, 0.563 mmol) and AIBN (15 mg, 0.091 mmol) (in one syringe) were added over 10 h via syringe pump to a stirred and refluxing solution of the selenide **157b** (159.2 mg, 0.433 mmol) in benzene (70 mL). Once addition was complete the solution was refluxed for an arbitrary time of 3 h. The reaction mixture was cooled to room temperature and concentrated. Flash chromatography of the crude products over silica gel (2 x 23 cm), using EtOAc-hexane mixtures (7 to 30% EtOAc), gave unreacted selenide **157b** [^{1}H NMR, 400 MHz)] (38.7 mg, 24.3 %), reduced product **159** (16.6 mg, 18%, 24% based on recovered selenide **157b**) as a pure [^{1}H NMR, (400 MHz)] oil, the product of β-scission (**158**) (7.6 mg, 8.3 %, 11% based on recovered selenide **157b**) as a fairly pure [ca. 90% as judged by ^{1}H NMR (400 MHZ)], oil, and the product of closure **193** (23.5 mg, 26%, 34% based on recovered selenide **157b**) as a pure [^{1}H NMR (400 MHZ)], oil. Compound **159** had: FT-IR ($CDCl_3$ cast) 2934, 2863, 1726, 1448, 1234, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (d, *J* = 7.5 Hz, 3 H), 1.21-1.75 (br m, 8 H), 1.82-2.00 (m, 2H), 2.01-2.10 (m, 1 H), 2.20-2.33 (m, 1 H), 2.35-2.46 (m, 1 H), 3.62 (s, 3 H), 9.72 (t, *J* = 1.5 Hz, 1 H); exact mass, *m/z* calcd. for $C_{12}H_{20}O_3$ 212.1412, found 212.1416. Compound **158** had: FT-IR ($CDCl_3$ cast) 2936, 2862, 1724, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, *J* = 7.5 Hz, 3 H), 1.20-2.00 (br m, 12 H, should be 10 H), 2.09-2.25 (m, 1 H), 2.56 (dd, *J* = 7.5, 1.5 Hz, 2 H), 3.65 (s, 3 H), 9.70 (t, *J* = 1.5 Hz, 1 H); exact mass, *m/z* calcd. for $C_{12}H_{20}O_3$ $[(M-H)]^+$ 211.1334, found 211.1344. Compound **193** had FT-IR (CH_2Cl_2 cast) 3120-3600 (br), 2928, 2859, 1730, 1458, 1197 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05-1.48 (m, 1 H), 1.52-1.80 (br m, 7 H), 1.97-2.15 (m, 2 H), 3.63 (s, 3 H), 4.00-4.12 (m, 1 H); ^{13}C NMR APT ($CDCl_3$, 75.5 MHz) δ 23.62 (t'), 26.62 (t'), 28.90 (t'), 30.27 (t'), 31.77 (t'), 36.53 (t'), 38.25 (t'), 38.37 (d'), 48.69 (s'), 51.11 (q'), 66.63 (d'), 176.03 (q'); exact mass, *m/z* calcd for $C_{12}H_{20}O_3$ [(M - H$^+$)]$^+$ 211.1334, found 211.1335. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.43; H, 9.69.

Triethyl Borane Cyclization at 0°C



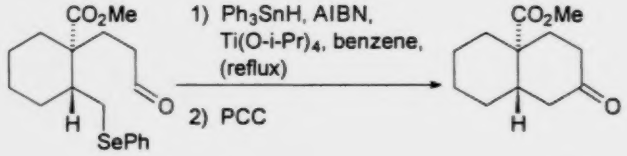
Ph_3SnH (210.0 mg, 0.576 mmol) in hexane (6 mL plus 2 mL as a rinse) and Et_3B (1.0 mL, 1M in hexane, 1.0 mmol) were added simultaneously over 15 sec to a stirred and cooled (0°C) solution of aldehyde **157b** (86.0 mg, 0.234 mmol) in hexane (40 mL). Air (20 mL) was then bubbled though the solution over 30 sec and stirring, without protection from the atmosphere, was continued for 4 h. At this point the reaction was still incomplete (TLC control, silica, 30% EtOAc-hexane). Ph_3SnH (50.0 mg, 0.142 mmol) in hexane (3 mL plus 1 mL as a rinse) and Et_3B (0.5 mL, 1M in hexane, 0.50 mmol) were added and stirring was continued for 4 h. evaporation of the solvent and flash chromatography of the crude products over silica gel (2 x 20 cm), using EtOAc-hexane mixtures of (10 to 30% EtOAc), gave the isomeric alcohols **192** and **193**, which were not characterized, but oxidized directly to ketone **166b**. PCC (155.0 mg, 0.702 mmol) and powdered 4 Å molecular sieves (20 mg) were added to a stirred solution of alcohols **192** and **193** in CH_2Cl_2 (10 mL) . The resulting mixture was stirred under argon for 9 h and then filtered though Celite (2 x 9) cm. The pad was washed with CH_2Cl_2 (20 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 8% EtOAc-hexane, gave ketone **166b** (19.4 mg, 39%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil.

Thermal Radical Cyclization with Triethyl Borane.



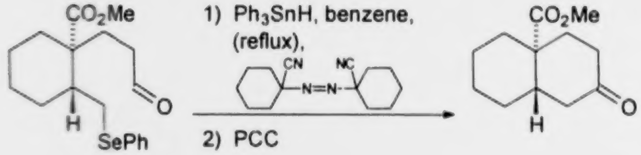
A benzene (5 mL) solution of Ph_3SnH (100.0 mg, 0.281 mmol) and AIBN (10 mg) were added over a 10 h period via syringe pump to a solution of selenide **157b** (79.5 mg, 0.216 mmol) and Et_3B (0.48 mL, 1M solution in hexane, 0.48 mmol) in benzene (35 mL). Once addition was complete the solution was refluxed for an arbitrary period of 3 h. The mixture was then cooled to room temperature and evaporated. Flash chromatography of the crude products over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (7 to 30% EtOAc), gave the product of reduction (**159**) (9.9 mg, 26%) as a pure [^{1}H NMR (400 MHZ)], oil, recovered **157b** (12.9 mg, 16%), as a pure [^{1}H NMR (400 MHZ)], oil, and alcohols **192** and **193** which were not characterized but oxidzied to ketone **166b**. PCC (140 mg, 0.648 mmol) and powdered 4 Å molecular sieves (30 mg) were added to a solution of alcohols **192** and **193** in CH_2Cl_2 (15 mL). The resulting mixture was stirred under argon for 12 h and filtered though Celite (2 x 9) cm. The pad was washed with CH_2Cl_2 (40 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 7% EtOAc-hexane, gave ketone **166b** (16.5 mg, 36%, 43% based on recovered **157b**) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil.

Thermal Radical Cyclization with Ti(O-*i*-Pr)$_4$



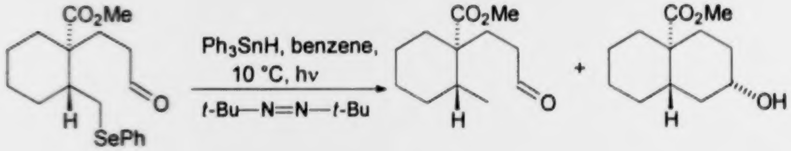
A benzene (10 mL) solution of Ph$_3$SnH (182.5 mg, 0.52 mmol) and AIBN (13 mg) were added over 10 h via syringe pump to a refluxing solution of selenide **157b** (159.2 mg, 0.433 mmol) and Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.88 mmol) in benzene (10 mL). After the addition was complete the solution was refluxed for an arbitrary period of 3 h. The reaction mixture was cooled to room temperature and concentrated. Flash chromatography of the crude products over silica gel (2 x 19 cm), using EtOAc-hexane mixtures (7 to 30% EtOAc), gave recovered selenide **157b** (45.8 mg, 31%) as a pure [^{1}H NMR (400 MHZ)], oil and alcohols **192** and **193**, which were not characterized but oxidzied to the ketone **166b**. PCC (260.0 mg, 1.20 mmol) and powdered 4 Å molecular sieves (100 mg) were added to a solution of alcohols **192** and **193** in CH$_2$Cl$_2$ (15 mL) . The resulting mixture was stirred under argon for 7 h and filtered though Celite (2 x 9 cm). The pad was washed with CH$_2$Cl$_2$ (20 mL) and the combined filtrates were evaporated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (7 to 20% EtOAc), gave ketone **166b** (6.2 mg, 11% based on recovered **157b**) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil.

Thermal Radical Cyclization with Azobiscyclohexylnitrile as Initiator.


CO2Me
1) Ph3SnH, benzene, (reflux),
CN
NC
N=N
H
SePh
2) PCC
O
CO2Me
H
O

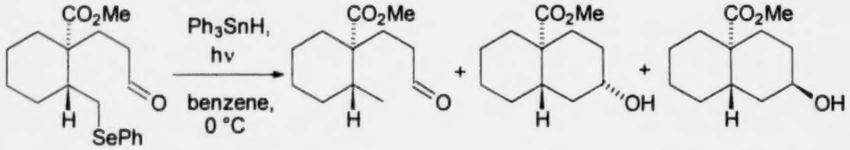
A benzene (10 mL) solution of Ph_3SnH (200.0 mg, 0.570 mmol) and azobiscycloheyxlnitrile (30 mg, 0.11 mmol) were added 10 h via syringe pump to a refluxing solution of selenide **157b** (136.3 mg, 0.371 mmol) in benzene (10 mL). After the addition the solution was refluxed for an arbitrary period of 8 h. The mixture was cooled to room temperature and concentrated. Flash chromatography of the crude products over silica gel (2 x 19 cm), using 7% EtOAc-hexane, gave product of direct reduction (**159**) (22.0 mg, 28%) as a pure [^{1}H NMR (400 MHZ)] oil, and axial alcohol **193** (17.2 mg, 22%) as a pure [^{1}H NMR (400 MHZ)] oil, and equatorial alcohol **192** (2 mg, 3%) as a pure [^{1}H NMR (400 MHZ)] oil.

Radical Cyclization with (bis)-*t*-butylazide as Photolytic Initiator.


CO2Me
H
SePh
O
Ph3SnH, benzene,
10 °C, hv
t-Bu—N=N—t-Bu
CO2Me
H
O
+
CO2Me
H
OH

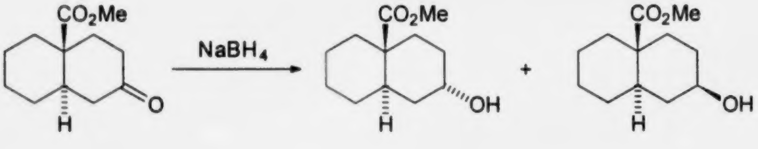
A cooled (10°C) benzene (10 mL) solution of Ph_3SnH (200.0 mg, 0.570 mmol), (bis)-*t*-butylazide (16 mg, 0.112 mmol), and selenide **157b** (44.8 mg, 0.122 mmol) in an optically flat round bottom flask was irradiated with a sunlamp (300 W) for 6 h. The reaction mixture was concentrated and flash chromatography of the crude products over silica gel (2 x 19 cm), using 7% EtOAc-hexane, gave recovered starting material (**157b**) (15.6 mg, 35%) as a pure [^{1}H NMR (400 MHZ)] oil and axial alcohol **193** (8.3 mg, 32%, 49% based on recovered **157b**) as a pure [^{1}H NMR (400 MHZ)] oil.

Photolysis Experiment without Initiator



A stirred and cooled (10°C) benzene (28 mL) solution of Ph_3SnH (155.0 mg, 0.295 mmol) and selenide **157b** (44.8 mg, 0.122 mmol) was irradiated with a sunlamp (300 W) for 6 h. The mixture was concentrated and flash chromatography of the crude products over silica gel (2 x 19 cm), using 7% EtOAc-hexane, gave the product of direct reduction (**159**) (9.8 mg, 15%) as a pure [^{1}H NMR (400 MHZ)] oil, axial alcohol **193** (31.8 mg, 51%) as a pure [^{1}H NMR (400 MHZ)] oil, and equatorial alcohol **192** (19.4 mg, 31%) as a pure [^{1}H NMR (400 MHZ)] oil.

Methyl (4aα, 8aβ)-decahydro-2β-hydroxynaphthalene-4a-carboxylate (192) and Methyl (4aα, 8aβ)-decahydro-2α-hydroxynaphthalene-4a-carboxylate (193).



$NaBH_4$ (100 mg, 2.51 mmol) was added in three portions over ca. 30 sec to stirred and a cooled (0°C) solution of the ketone **166b** (85.3 mg, 0.406 mmol) in dry

MeOH (10 mL). No starting material remained after 5 min (TLC silcia, 30% EtOAc-hexane). Aqueous HCl (20 mL, 20%) was added dropwise to the stirred and cooled solution until effervescence ceased. The solution was extracted with Et_2O (3 x 30 mL), dried, and concentrated. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 15% EtOAc-hexane, gave alcohol **193** (3.7 mg, 4%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)] oil which was identical to the major product obtained from thermal radical cyclization, and **192** (67.3 mg, 78%) as a pure [TLC, silica, 30% EtOAc-hexane, ^{1}H NMR (400 MHz)], oil: FT-IR (CH_2Cl_2 cast) 2927 (br), 2858, 1731, 1455, 1414 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95-1.29 (br m, 5 H), 1.30-1.40 (br d, J = 13 Hz, 1 H), 1.50-1.59 (br d, J = 17 Hz, 1 H), 1.61-1.90 (br m, 6 H), 1.96-2.09 (dd, J = 11, 3 Hz, 2 H), 3.50-3.66 (m, including s at δ 3.61, 4 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 23.40 (t'), 22.65 (t'), 29.00 (t'), 32.82 (t'), 36.35 (t'), 37.83 (t'), 38.81 (t'), 43.29 (t'), 47.75 (s'), 51.17 (s'), 70.80 (d'), 175.68 (s'); exact mass, *m/z* calcd for $C_{12}H_{20}O_3$ 212.1386, found 212.1408. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.82; H, 9.58.

REFERENCES

1. (a) Jasperse, C.P; Curran, D.P.; Fevig, T.L. *Chem. Rev.* **1991**, *91*, 1237; (b) Curran, D.P. "Radical Cyclizations and Sequential Radical Reactions" in *Comprehensive Organic Synthesis: Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*, Fleming, I. and Trost, B. Eds.; Vol. 4, 1991, 779. (c) Curran, D.P. *Synthesis* **1988**, 417; (d) Curran, D.P. *Synthesis* **1988**, 489; (e) Beckwith, A.L.J. *Tetrahedron* **1981**, *37*, 3073.
2. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.
3. Tsang, R.; Dickson, J.K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484.
4. Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* **1989**, *111*, 230.
5. Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* **1989**, *111*, 2674.
6. Beckwith, A.L.J.; Raner, K.D. *J. Org. Chem.* **1992**, *57*, 4954.
7. Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791.
8. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.
9. Dickson, J.K.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440.
10. Anissa Yeung, B.-W.; Alonso, R.; Vite, G.D.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1989**, *8*, 413.
11. Jung, M.E.; Choe, T.S.W. *Tetrahedron Lett.* **1993**, *34*, 6247.
12. Knapp, S.; Gibson, F.S. *J. Org, Chem.* **1992**, *57*, 4802.
13. Kiyooka, S.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org, Chem.* **1990**, *55*, 5562.
14. Curran, D.P,; Liu, H. *J. Org. Chem.* **1991**, *56*, 3463.
15. Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515.
16. Tsai, Y.-M.; Tang, K.-H.; Jiang, W.T. *Tetrahedron Lett.* **1993**, *34*, 1303.

17. Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

18. Beckwith, A.L.J.; O'Shea, D.M.; Westwood, S.W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

19 Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77.

20. Dowd, P.; Choi, S.-C. *Tetrahedron* **1991**, *47*, 4847.

21. Dowd, P.; Choi, S.-C. *J.Am. Chem. Soc.* **1987**, *109*, 9548.

22. Nishida, A.; Takahashi, H.; Takeda, H.; Tekada, N.; Yonemitsu, O. *J. Am. Chem. Soc.* **1990**, *112*, 902.

23. Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *52*, 7163.

24. Zhang, W.; Dowd, P. *Tetrahdron Lett.* **1992**, *33*, 3285.

25. Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1404.

26. Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295.

27. Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143.

28. Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H.; Ogawa, A.;; Sonoda, N. *Tetrahedron Lett.* **1990**, *31*, 6887.

29. Ryu, I.; Kusano, K.; Yamazaki, H.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5003.

30. Ryu, I.; Yamazaki, H.; Kusano, K.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 8558.

31. Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115,* 1187.

32. Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018.

33. Clive, D.L.J.; Cheshire, D.R.; Set, L. J. *Chem. Soc., Chem. Commun.* **1987**, 353.

34. Clive, D.L.J.; Manning, H.W.; Boivin, T.L.B.; Postema, M.H.D. *J. Org. Chem.* **1993**, *58*, 6857.

35. Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.

36. Bergstra, R.J. Ph.D. Thesis, University of Alberta, **1991**.

37. Villieras, J.; Rambaud, M. *Synthesis* **1983**, 924.

38. Olah, G.A.; Karpelas, R.; Narang, S.C. *Synthesis* **1982**, 963.

39. Kolb, M.; Barth, J. *Synth. Commun.* **1981**, *11*, 763.

40. Knochel, P.; Normant, J.F. *Tetrahedron Lett.* **1985**, *24*, 425.

41. Ward, D. Kaller, B.F. *Tetrahedron Lett.* **1991**, *32*, 843.

42. Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

43. Ochiai, M.; Nishide, K.; Node, M.; Fujita, E. *Chem. Lett.* **1981**, 283.

44. Canonne, P. ; Akssira, M. *Tetrahedron* **1985**, *41*, 3695.

43. Ochiai, M.; Nishide, K.; Node, M.; Fujita, E. *Chemistry Lett.* **1981**, 283.

45. Hartford Manning and Derek Cole personal communications.

46. Marino, J.P.; Laborde, E.; Paley, R.S. *J. Am. Chem. Soc.* **1988**, *110*, 966.

47. Jacobson, R.M.; Raths, R.A.; McDonald, J.H. III *J. Org. Chem.* **1977**, *42*, 2545. See also reference 12 and references cited therein for the preparation of a similar compound.

48. Larson, G.L.; Kleese, R. *J. Org. Chem.* **1985**, *50*, 3627.

49. Knapp, S.; Gibson, F.S.; Choe, Y.H. *Tetrahedron Lett.* **1975**, 499.

50. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6127; (b) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547; (c) Barton, D.H.R.; Jang, D.O.; Jasberenyi, J. Cs. *Tetrahedron Lett.* **1990**, *31*, 4681.

51. Levine, S.G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.

52. Commercially available from Aldrich.

53. Pereyre, M.; Quintard, J.-P.; Rahn, A. *Tin in Organic Synthesis*, Butterworths, London, 1987.

54. *Tables of Spectral Data for Structure Determination of Organic Compounds* Springer-Verlag, London, 1987, C-71.

55. Nogradi, M *Stereoselective Synthesis*, VCH Press, New York, 1987.

56. Smith, J.G.; Dibble, D.W.; Sandborn, R.E. *J. Org, Chem.* **1986**, *51*, 3762.

57. Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

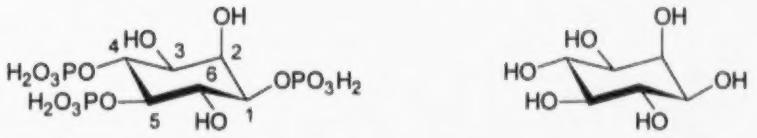
58. D.H.R. Barton; Lester, D.J.; Motherwell, W.B.; Papoula, M.T.B. *J. Chem. Soc., Chem. Commun.* **1980**, 246.

Chapter 3

Synthetic StudiesTowards Inositol (D)-1,4,5-Triphosphate

INTRODUCTION

The subject of inositol chemistry has grown widely over the last eight years, as is evident from the excellent book recently written by Billington.[1] Although there exists a large literature on the biological activity of inositol phosphates this review will focus on a few of the more recent synthetic approaches[2] to inositol 1,4,5-triphosphate (**1**) (1,4,5-IP_3) and will outline the different strategies employed to synthesize this molecule. Inositol (-)-1,4,5-triphosphate is commercially available as the hexasodium salt for a price of $600.00 per milligram.[3]

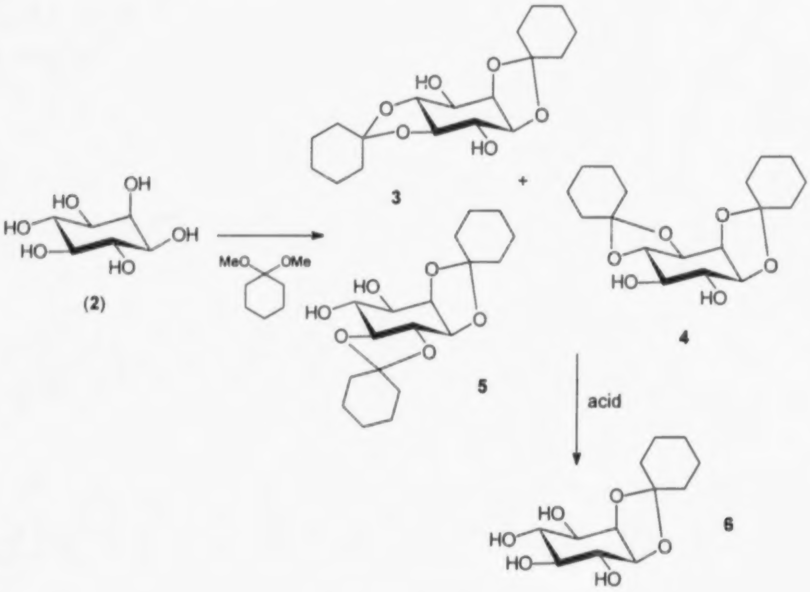


D-(-)-inositol 1,4,5-triphosphate, D-1,4,5-IP_3 (**1**) *myo*-inositol (**2**)

Figure III-1

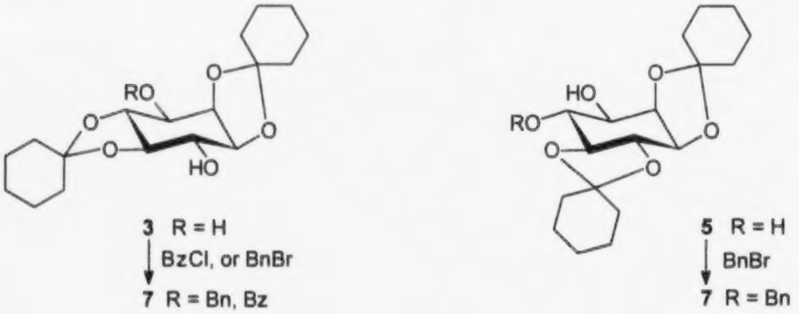
The biological action of 1,4,5-IP_3 is to act as a secondary messenger that targets specific receptors in the cell and causes the release of calcium.[4] Before a detailed discussion of synthetic approaches to 1,4,5-IP_3 is presented, some background on inositol chemistry will be discussed.

If the phosphate groups are removed from 1,4,5-IP_3 one obtains *myo*-inositol (**2**) a *meso* compound. Many of the published synthetic approaches to 1,4,5-IP_3 begin with *myo*-inositol, since it is inexpensive and readily available. There is one problem with this approach; the starting material is not chiral and therefore to be able to efficiently produce naturally occurring (-)-1,4,5-IP_3 a resolution step or the use of chiral reagents is required. If (**2**) is ketalized with cyclohexanone (or derivatives thereof) one obtains a separable mixture of three compounds **3**, **4**, and **5**, all of which can be selectively hydrolyzed to the monoketal **6**, Scheme III-1.[5]


(2)
MeO OMe
3
+
4
5
acid
6
HO
OH
O

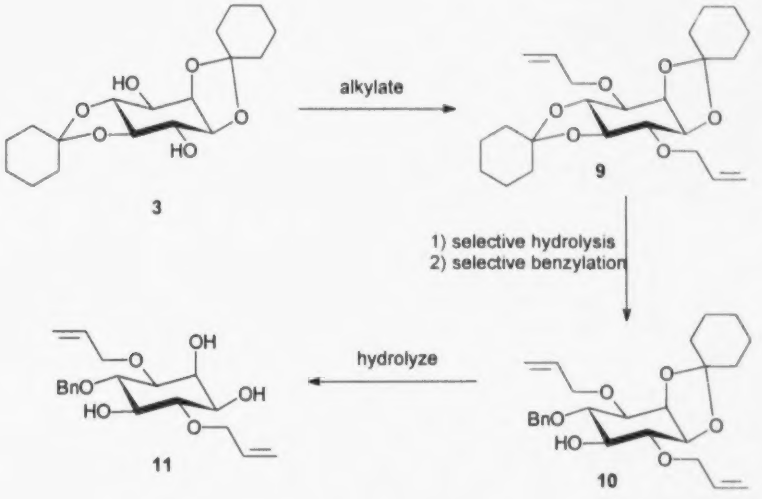
Scheme III-1

These compounds are quite versatile intermediates since both **3** and **4** can be selectively protected as shown below in Scheme III-2.

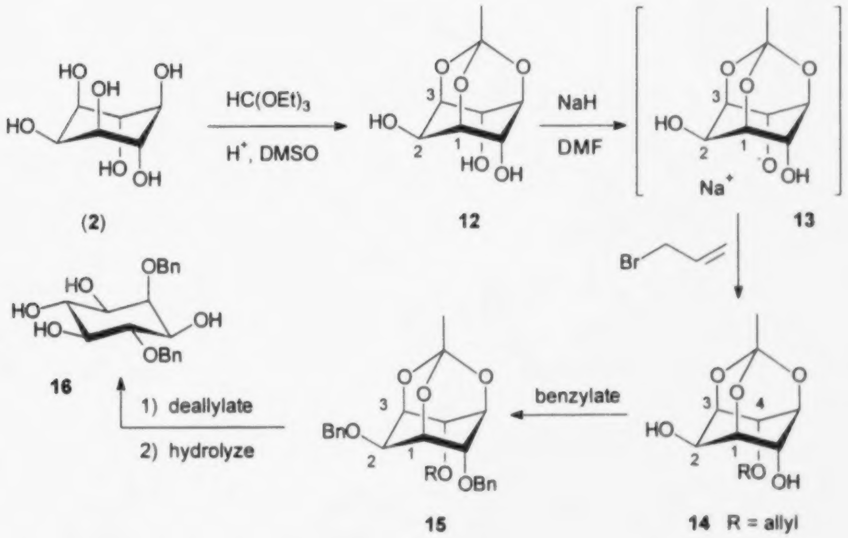

RO
HO
O
3 R = H
BzCl, or BnBr
7 R = Bn, Bz
5 R = H
BnBr
7 R = Bn

Scheme III-2

Once the acid-stable protecting group(s) have been installed, selective deketalization can be carried out, thereby allowing for further chemistry. Scheme III-3 illustrates such a strategy.


HO
HO
3
alkylate
9
1) selective hydrolysis
2) selective benzylation
hydrolyze
OH
BnO
HO
OH
11
BnO
HO
10

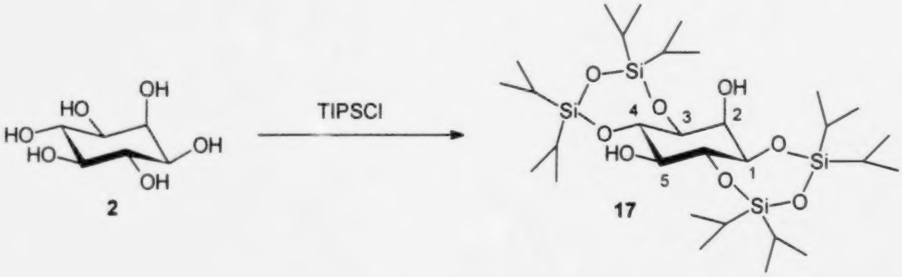
Scheme III-3


HO
OH
OH
HO
HO
OH
(2)
HC(OEt)$_3$
H$^+$, DMSO
12
NaH
DMF
Na$^+$
13
Br
OBn
HO
HO
HO
OH
OBn
16
1) deallylate
2) hydrolyze
BnO
RO
OBn
15
benzylate
HO
RO
OH
14 R = allyl

Scheme III-4

An alternative strategy[6] that has seen use in inositol synthesis is the orthoformate route. Treatment of *myo*-inositol with triethylorthoformate under acid catalysis in DMSO gives the 1,3,5-orthoformate **12** (Scheme III-4). The alkylation of inositol orthoformate is highly selective. Treatment with sodium hydride in DMF gives an anion that is stabilized by internal coordination to yield, upon exposure to allyl bromide for example, the monoallyl derivative **14**. The 2 and 6 positons can now be benzylated, and removal of the orthoester and the allyl group produces tetrol **16**.

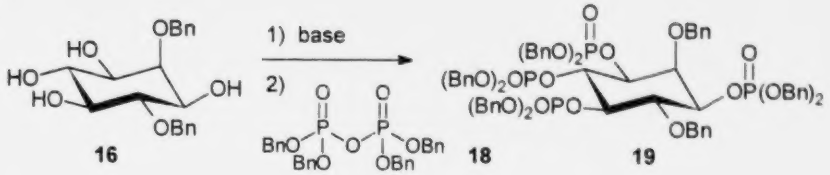
Reaction of (**2**) with TIPSCl (2.5 eq.) gives the diol **17**, in which the 2 and 5 hydroxyls have been left open (Scheme III-5).[7] This strategy compliments the ketalization approach discussed earlier.



Scheme III-5

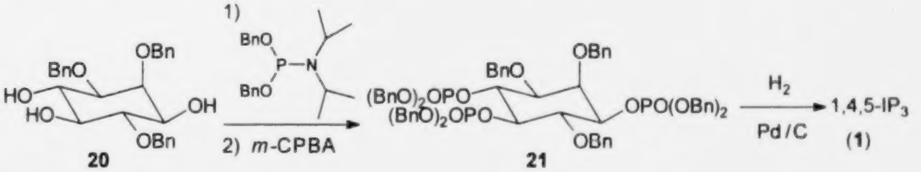
Synthesis of 1,4,5-IP$_3$

Several approaches to the synthesis of (**1**) have relied on the fact that triol **16** can be converted to 1,4,5-IP$_3$ by phosphorylation. Two main strategies have been developed to effciently introduce the phosphate group(s). The first (showing the synthesis of a tetraphosphate) involves the reaction of an alkoxide polyanion with tetrabenzylpyrophosphate (TBPP) **18**.[8]



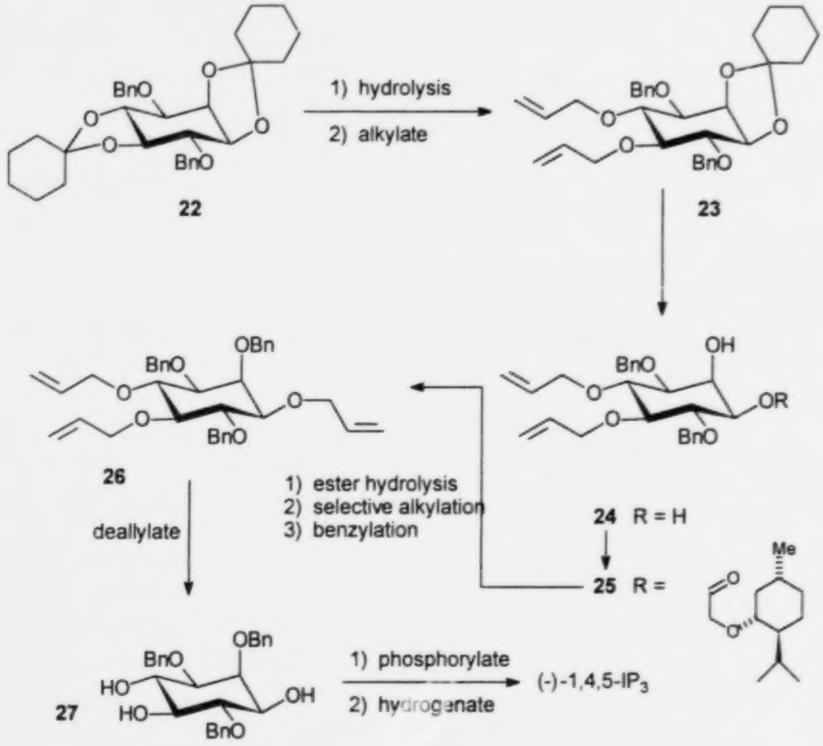
Scheme III-6

The second method is to alkylate with a phosphorous (III) species and to oxidize the resulting phosphite ester to a phosphate ester through the use of *m*-CPBA or another peroxide.[9] Different leaving groups on phosphorous have been used these include halogens or amines. For example, the triol **20** was phosphorylated by reaction with the amino phosphite and this was followed by oxidation of the phosphite ester to the fully protected phosphate **21**. Hydrogenation then furnished racemic 1,4,5-IP_3 (**1**).[9a]



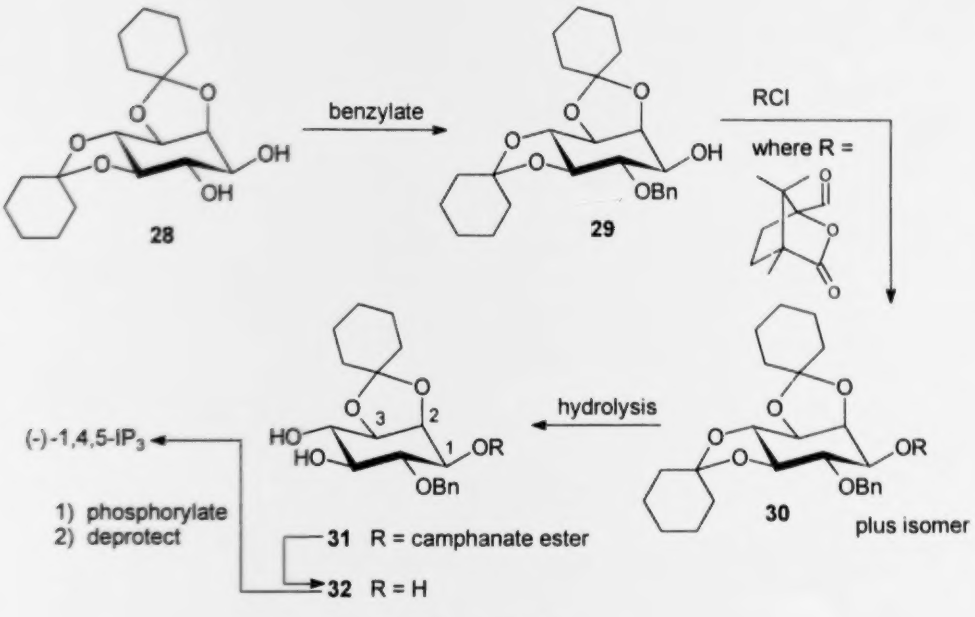
Scheme III-6

The first reported total synthesis was accomplished by Ozaki in 1986.[10] The fully protected derivative **22** underwent selective ketal hydrolysis and the resulting diol was alkylated to give **23**. The remaining ketal was removed, and selective acylation of the more reactive equatorial alcohol with a menthol derived chiral unit gave a mixture of two diastereomers that were separated to afford the desired product **25**. The ester group was exchanged for an allyl group and the remaining free hydroxyl group was benzylated. Removal of all three allyl groups then gave triol **27**. Phosphorylation and hydrogenation then gave (-)-1,4,5-IP_3 (Scheme III-7). The key steps in this sequence include the selective differentiation between *O*-1 and *O*-2, which was discovered by Gigg,[5] over twenty years ago, and the resolution using the available menthol derivative **25**.


BnO
BnO
22
1) hydrolysis
2) alkylate
BnO
BnO
23
OH
BnO
OR
BnO
24 R = H
25 R =
Me
OBn
BnO
BnO
26
1) ester hydrolysis
2) selective alkylation
3) benzylation
deallylate
OBn
BnO
HO
HO
OH
BnO
27
1) phosphorylate
2) hydrogenate
(-)-1,4,5-IP3

Scheme III-7

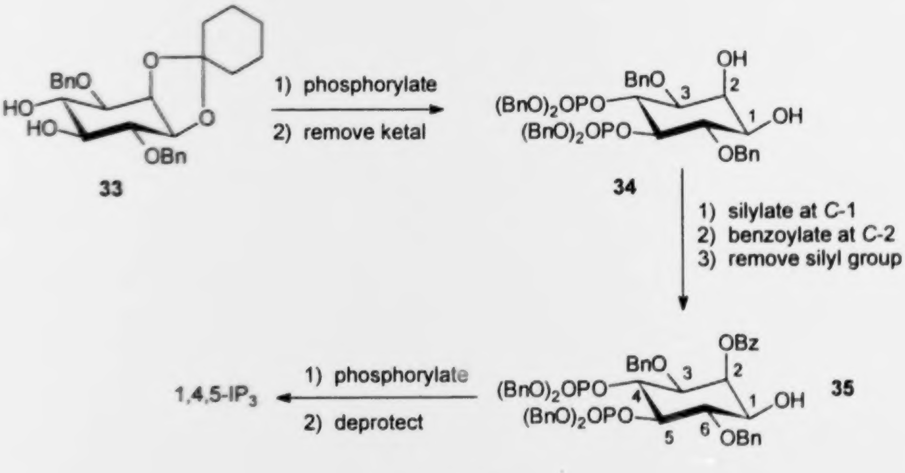
An alternative, but conceptually similar, approach is outlined in Scheme III-8. Ketal **28** was selectively benzylated, and resolution via the camphanate ester gave optically pure **30**. The *trans* ketal was selectively hydrolyzed to give triol **32** in which the 1, 4, and 5-hydroxyl groups are free. Phosphorylation, hydrogenation, and acid removal of the ketal then produced (-)-1,4,5-IP_3.[11]



28
benzylate
29
RCl
where R =
30
plus isomer
hydrolysis
(-)-1,4,5-IP3
1) phosphorylate
2) deprotect
31 R = camphanate ester
32 R = H
OH
OBn
OR
HO

Scheme III-8

Most of the approaches towards 1,4,5-IP$_3$ include phosphorylation at the end of the sequence. Ozaki also used an early phosphorylation strategy in his synthesis of racemic 1,4,5-IP$_3$ (Scheme III-9).[12]

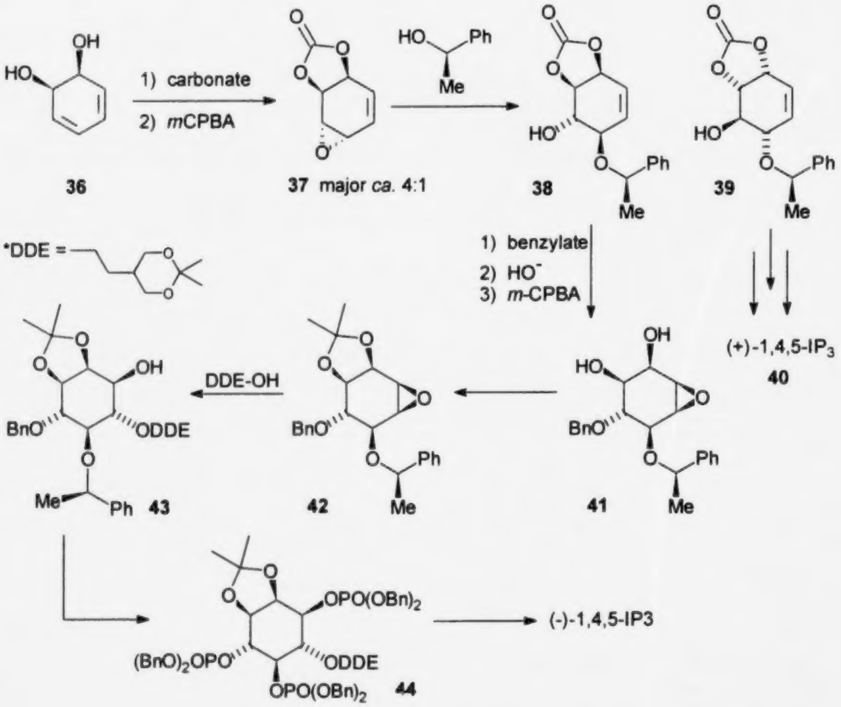


33
1) phosphorylate
2) remove ketal
34
1) silylate at C-1
2) benzoylate at C-2
3) remove silyl group
35
1,4,5-IP3
1) phosphorylate
2) deprotect
BnO
HO
OBn
OH
OBz
(BnO)2OPO

Scheme III-9

Diol **33** (made from **3** along lines shown in Scheme III-3) was phosphorylated and the ketal was removed to give diol **34**. *O*-2 was protected as its benzoyl ester by first protecting *O*-1, benzoylating *O*-2 and then removing the silicon protecting group from *O*-2. Further phosphorylation at *O*-1 followed by deprotection then gave racemic 1,4,5-IP$_3$.

Ley and co-workers[13] developed a unique approach to 1,4,5-IP$_3$ starting from benzene. The meso diol **36** (available by microbial oxidation of benzene) was protected as a cyclic carbonate, which underwent epoxidation with *m*-CPBA to give **37** as the major isomer (4:1).

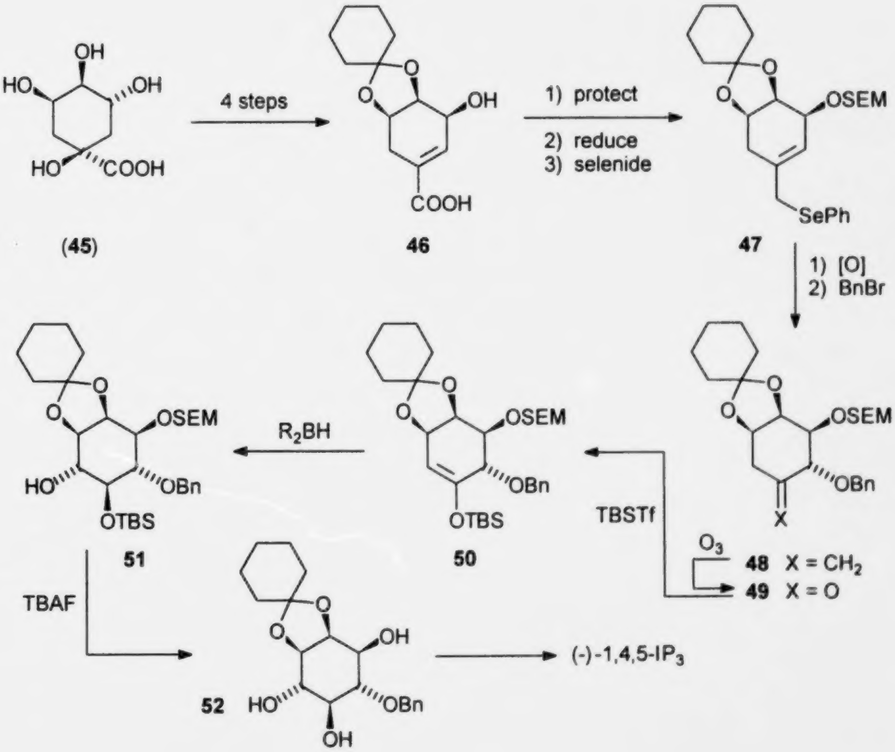


1) carbonate
2) mCPBA
HO Ph Me
36
37 major ca. 4:1
38
39
•DDE =
1) benzylate
2) HO⁻
3) m-CPBA
(+)-1,4,5-IP3
40
DDE-OH
43
42
41
44
(-)-1,4,5-IP3
OH
ODDE
BnO
OPO(OBn)2
(BnO)2OPO

Scheme III-10

Epoxide opening with (*R*)-(+)-*sec*-phenylethyl alcohol under acidic conditions gave a mixture of separable diastereomers **38** and **39**. Compound **38** was benzylated and deprotected. Directed epoxidation (*m*-CPBA) then gave **42**, after reprotection of the diol as its acetonide. Regioselective ring opening with the protected alcohol (DDEOH) furnished alcohol **43** with the correct relative and absolute configuration for conversion to (-)-1,4,5-IP$_3$. This was accomplished by benzyl group removal, phosphorylation and deprotection to give the target. It is noteworthy that the chiral protecting group is cleaved under similar conditions to that required for benzyl group removal. The other isomer (**39**) obtained in the resolution step was conveterd to (+)-1,4,5-IP$_3$ by similar chemistry.

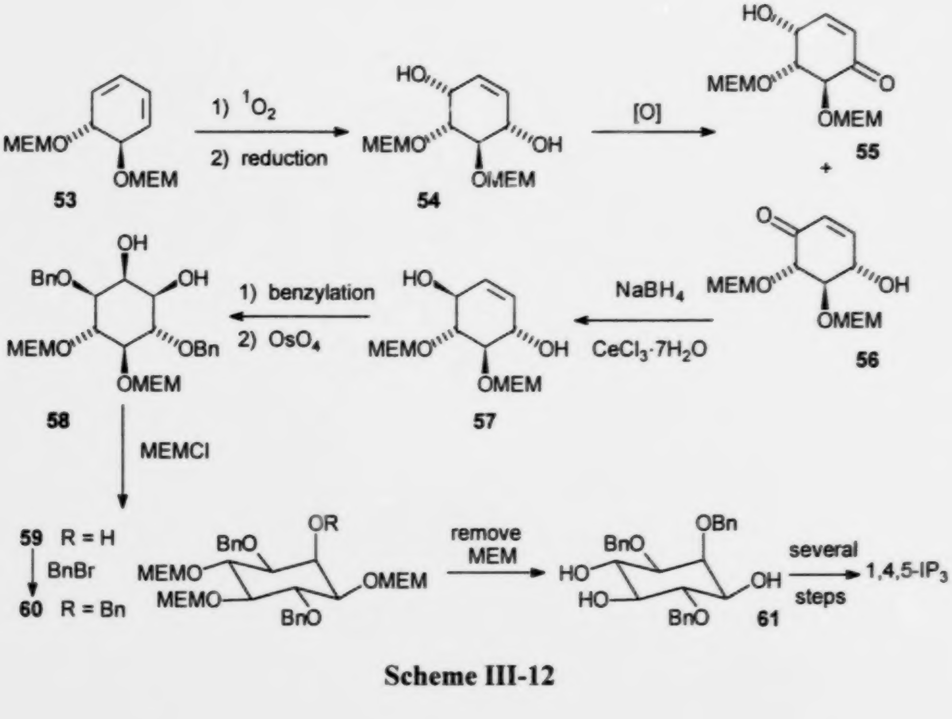
Falck[14] also used a non-inositol route in his synthesis of 1,4,5-IP$_3$. He chose to begin with (-)-quininc acid (**45**) which was converted into **46** in four steps according to a literature procedure (Scheme III-11).


(45)
4 steps
46
1) protect
2) reduce
3) selenide
47
1) [O]
2) BnBr
48 X = CH2
49 X = O
O3
TBSTf
50
R2BH
51
TBAF
52
(-)-1,4,5-IP3
OH
HO
COOH
OSEM
OBn
OTBS
SePh
X

Scheme III-11

Protection of the free hydroxyl was followed by reduction of the acid and conversion to allylic selenide **47**. Oxidation to the selenoxide was followed by [3,3] rearrangement to furnish the transposed alcohol, and this was benzylated to provide **48**. Oxidative cleavage of the olefin was followed by regioselective formation of silyl enol ether **50**, that then underwent hydroboration to **51**. The sequence was completed by removal of the silyl protecting groups to give triol **52**, which was converted to (-)-1,4,5-IP$_3$.

The approach of Carless and Busia[15] (Scheme III-12) commenced with **53**. Addition of singlet oxygen, followed by reduction of the oxygen-oxygen bond, afforded diol **54**. Oxidation gave two compounds, **55** and **56**, of which **56** was reduced to **57**. Benzylation was followed by *syn*-dihydroxylation to deliver diol **58**, which was selectively protected to give **59** and **60**. Removal of the MEM groups then gave racemic triol **61** which was converted to racemic 1,4,5-IP$_3$ by standard methods.

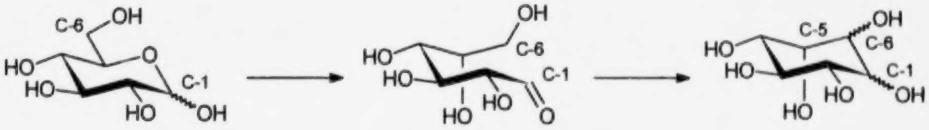


MEMO
OMEM
53
1) $^1O_2$
2) reduction
HO
MEMO
OH
OMEM
54
[O]
HO
MEMO
O
OMEM
55
+
O
MEMO
OH
OMEM
56
NaBH$_4$
CeCl$_3$·7H$_2$O
HO
MEMO
OH
OMEM
57
1) benzylation
2) OsO$_4$
OH
BnO
OH
MEMO
OBn
OMEM
58
MEMCl
59 R = H
BnBr
60 R = Bn
OR
BnO
MEMO
MEMO
OMEM
BnO
remove MEM
OBn
BnO
HO
HO
OH
BnO
61
several steps
1,4,5-IP$_3$

Scheme III-12

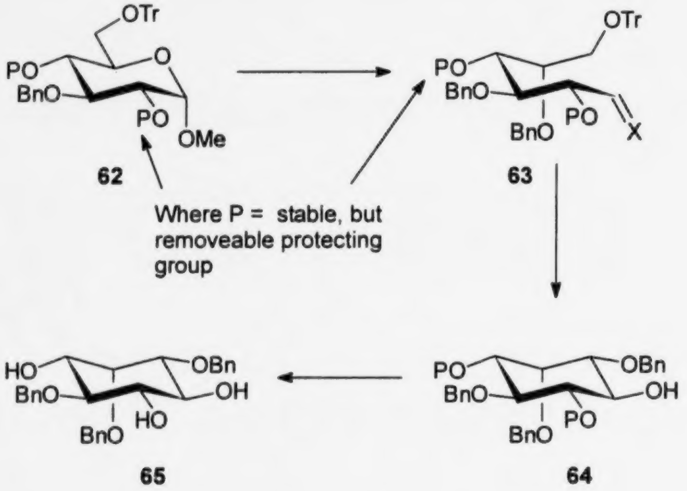
RESULTS and DISCUSSION

Almost all of the published synthetic approaches towards inositol 1,4,5-triphosphate (1,4,5-IP$_3$) (**1**) utilize *myo* inositol as the starting material.[1] Although other appoaches have started with six-membered ring structures, no published approach involved cyclizing a suitably functionalized chain to gain access to 1,4,5-IP$_3$.[16] We envisioned 1,4,5-IP$_3$ as being available from a cyclization reaction of *C*-1 and *C*-6 of a suitably modified D-glucose derivative (Scheme III-13).



Scheme III-13

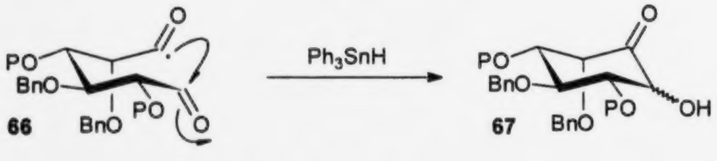
In its pyranose form, D-glucose has all its substituents equatorial. If *C*-6 is cyclized onto *C*-1 then *O*-5 now becomes axial and all that remains (assuming suitable *O*-protection) in order to synthesize (1,4,5-IP$_3$) is to ensure that the oxygen functions at *C*-1 and *C*-6 are equatorial. Naturally, differential protection of the appropriate hydroxyl groups is necessary since the unprotected target is a *meso* compound. After inspection of models, it was decided that the appropriate protecting group pattern would be as shown in Scheme III-14. At this juncture we had not yet decided on which type of ring closure we would examine first, although there were several options open to us. Our strategy needed to be flexible enough so that if one route failed we would not have to alter the sequence too much in order to try other approaches. Another self-imposed requirement was that our route should be amenable to the preparation of different analogs of (**1**) or other phosphorylated inositols. The general strategy shown in Scheme III-14 does, in principle, satisfy the above criteria. The chemistry of D-glucose is a well-developed area, and therefore many different protection patterns leading to various phosphorylated inositol derivatives should be possible. The general structure of intermediate **63** is such that it should be amenable to transformation into various derivatives.


OTr
PO
BnO
O
PO
OMe
62
OTr
PO
BnO
BnO
PO
X
63
HO
BnO
BnO
HO
OBn
OH
65
PO
BnO
BnO
PO
OBn
OH
64

Where P = stable, but removeable protecting group

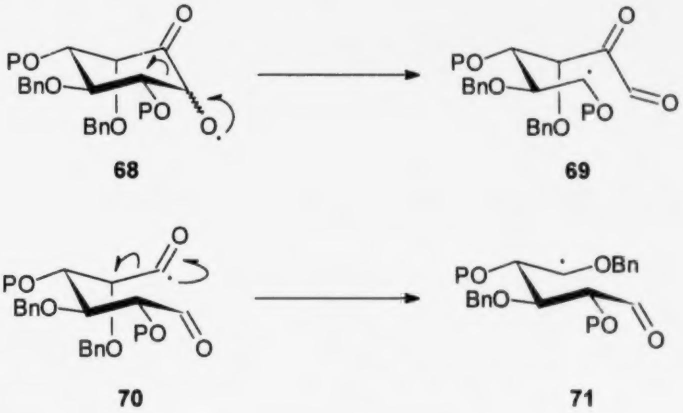
Scheme III-14

We initially envisioned a radical cyclization route, involving closure of an acyl radical onto the *C*-1 aldehyde to give the α-ketol system **67** (eq. III-2).


O
PO
BnO
66
BnO
PO
O
Ph3SnH
O
PO
BnO
67
BnO
PO
OH

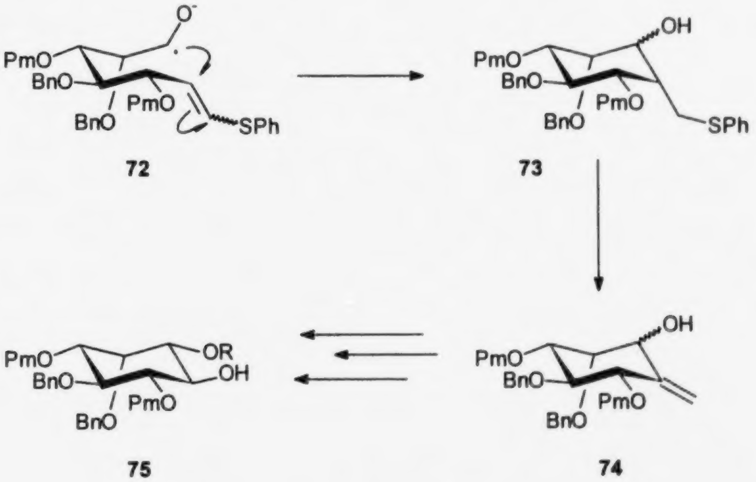
eq. III-2

Preliminary studies on simple alkyl radicals, using the borane method, showed that this was probably not feasible, since the formed alkoxy radical was prone to fragmentation (**68**→**69**) due to the stability of the formed radical. We were also concerned about premature decarbonylation (**70**→**71**) to give another stable α-oxygen radical (Scheme III-15).


PO
BnO
BnO
PO
O
68
69
70
71
OBn

Scheme III-15

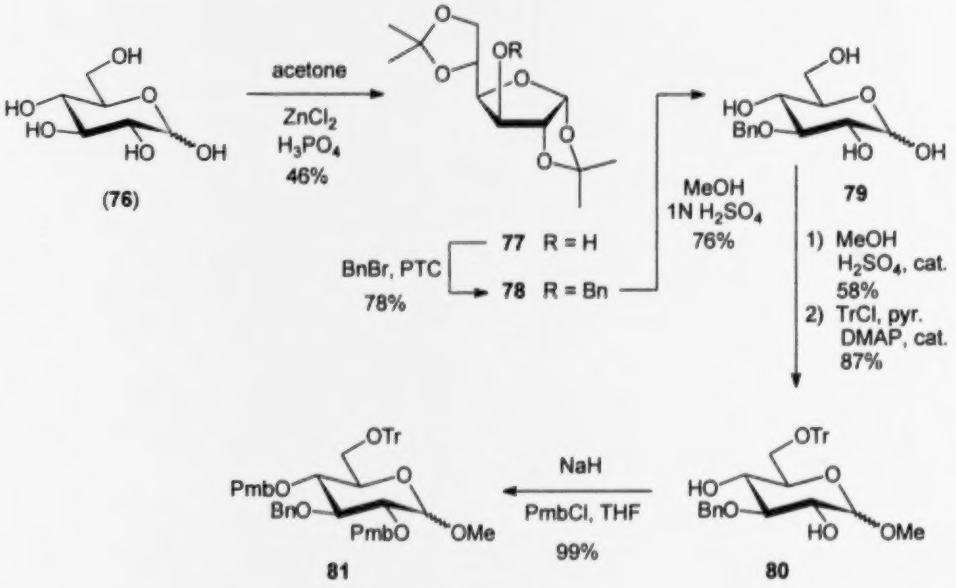
We finally decided to examine closure of a ketyl radical (or the corresponding acyl radical) onto a vinyl sulfide[17] (Scheme III-16).


PmO
BnO
BnO
PmO
SPh
OH
OR
72
73
74
75

Scheme III-16

The *p*-methoxybenzyl group seemed well suited to such an approach since it is fairly stable and can be selectively removed in the presence of other commonly-used protecting groups. Our target now becomes compound **72** (Scheme III-16). From our experience with stabilized radicals, the electron rich olefin seemed to be a suitable radical acceptor. The adduct sulfide **73** could be oxidized and fragmented to give an exocyclic olefin (**73**→**74**), that could potentially be transformed into the required equatorial hydroxyl group by oxidative cleavage of the olefin and subsequent stereoselective reduction (**74**→**75**).

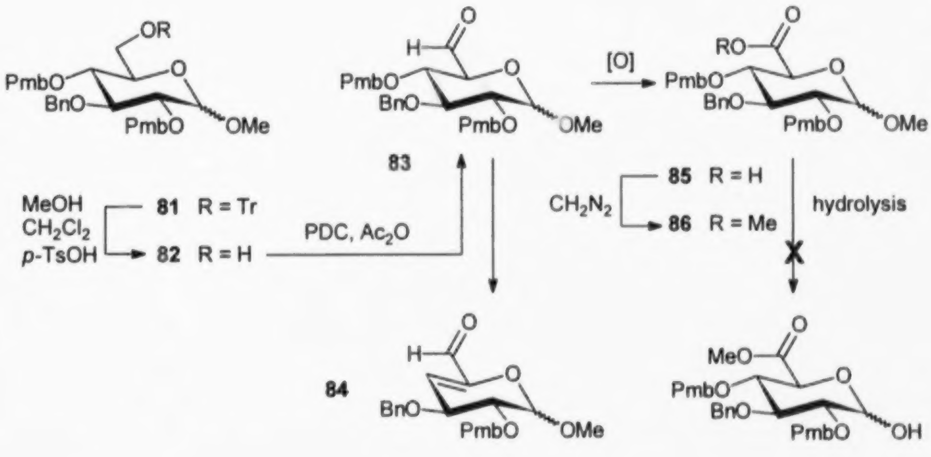
We now turned our attention to the actual preparation of **72**. We needed a *gluco* derivative that was differentially protected at *O*-1, *O*-2, *O*-4, and *O*-6. We therefore began with diacetone glucose **77**.


OH
HO
HO
HO
OH
O
(76)
acetone
ZnCl2
H3PO4
46%
OR
O
77 R = H
78 R = Bn
BnBr, PTC
78%
MeOH
1N H2SO4
76%
HO
BnO
79
1) MeOH
H2SO4, cat.
58%
2) TrCl, pyr.
DMAP, cat.
87%
OTr
HO
BnO
HO
OMe
80
NaH
PmbCl, THF
99%
PmbO
BnO
PmbO
OMe
81

Scheme III-17

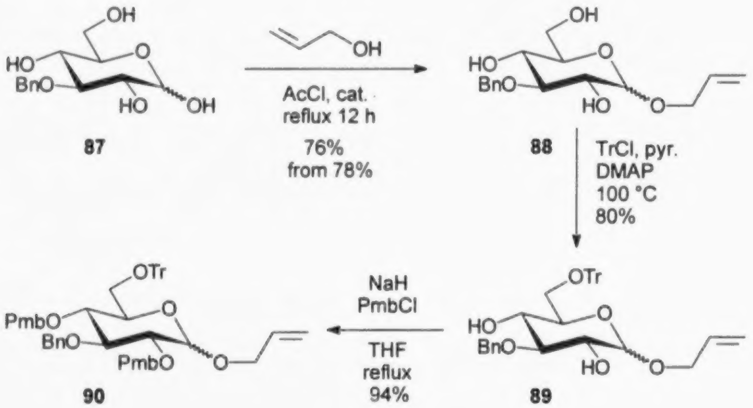
Ketalization of D-glucose according to a literature procedure[18] was followed by benzylation under phase transfer conditions[19] to furnish **78**. Acid hydrolysis[20] then provided **79**. We assumed at this stage that the methyl glycoside would be suitable for our purposes, since anomeric hydrolysis should be possible.

Accordingly, Fischer glycosidation with methanol paved the way for selective *O*-6 tritylation which was followed by protection of the two remaining free hydroxyl groups with *p*-methoxybenzyl chloride to provide the fully blocked derivative **81** (Scheme II-17). We now needed to deprotect *O*-6 and oxidize the resulting hydroxyl to either the ester or aldehyde level. Since two step oxidations to the acid are known to be reliable, **81** was detritylated and oxidized with PDC to give aldehyde **83** in 78% yield. Oxidation to the acid proved troublesome, as only low yields of ester (after treatment with diazomethane) were obtained. Also, aldehyde **83** was not very stable, and handling caused elimination to olefin **84**. Anomeric hydrolysis of **86** became a problem since the *p*-methoxybenzyl protecting groups were hydrolyzed at a similar rate to the anomeric methyl group.



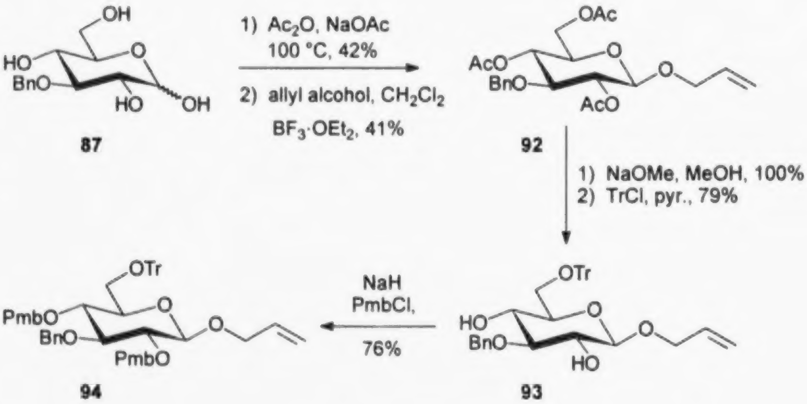
Scheme III-18

We then turned to a modified route, as outlined in Scheme III-19. We decided to change the anomeric protecting group to allyl and to keep *O*-6 protected until such a point when it would be desirable to carry out the oxidation step. We carried out two versions of this sequence, one with a mixture of anomers and the other with the β-anomer only. The reason for this approach was to simplify characterization of the intermediates. Compound **88** was exposed to Fischer glycosidation conditions, tritylated, and benzylated to give **90** (Scheme III-19).


OH
HO
BnO
O
HO
OH
87
OH
AcCl, cat.
reflux 12 h
76%
from 78%
88
TrCl, pyr.
DMAP
100 °C
80%
OTr
89
NaH
PmbCl
THF
reflux
94%
PmbO
90

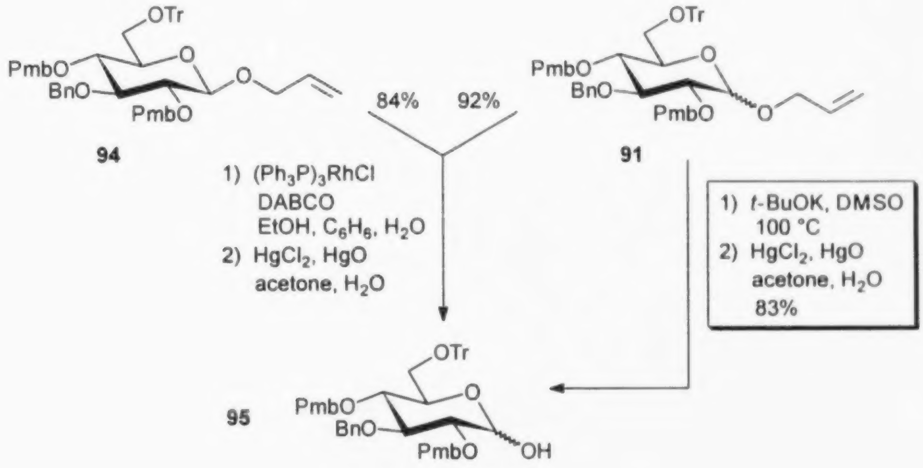
Scheme III-19

The β-anomer was made via acetate **92**[22] as shown in Scheme III-20.

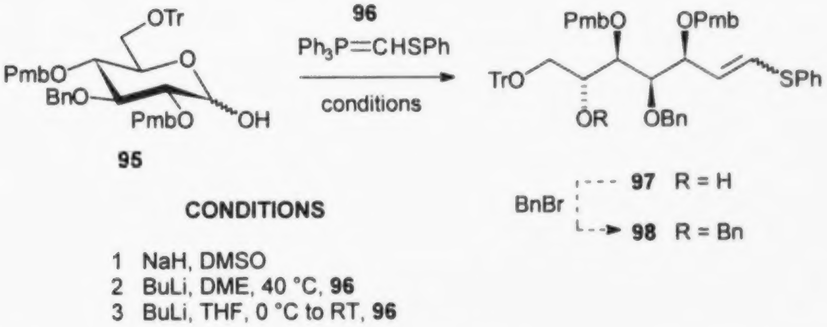

87
1) Ac_2O, NaOAc
100 °C, 42%
2) allyl alcohol, CH_2Cl_2
$BF_3 \cdot OEt_2$, 41%
OAc
AcO
92
1) NaOMe, MeOH, 100%
2) TrCl, pyr., 79%
93
NaH
PmbCl,
76%
94

Scheme III-20

We initially utilized Wilkinsons catalyst[23] to isomerize the allyl group and we then hydrolyzed the resulting enol ethers via the mercury method.[24] The anomeric mixture **90** and the β-anomer **94** both gave the same mixture of lactols (**95**) upon exposure to these conditions (Scheme III-21). It was later found that the isomerization procedure,[25] using potassium *t*-butoxide in DMSO at 110°C followed by mercuric-catalyzed hydrolysis, worked equally well, and was most cost effective and this is the method we used from that point on.

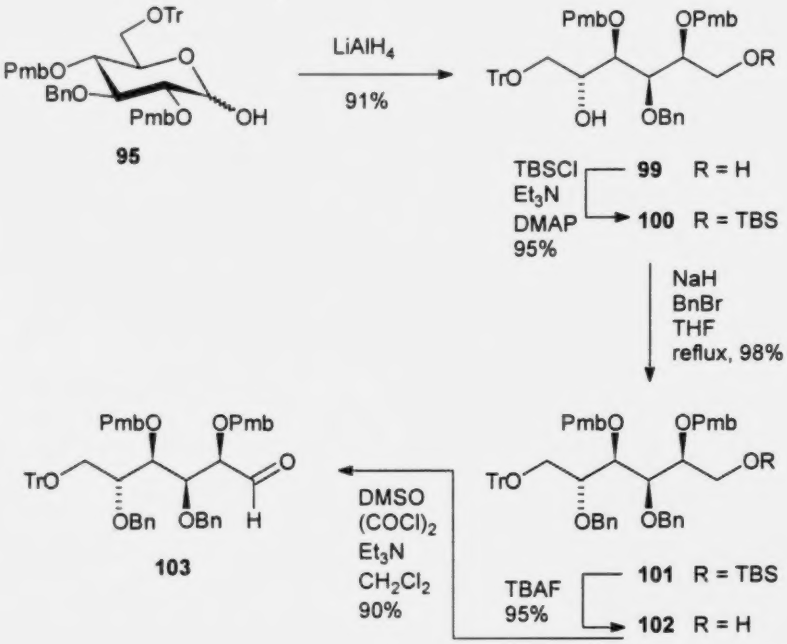

OTr
PmbO
BnO
PmbO
94
84%
92%
91
1) $(Ph_3P)_3RhCl$
DABCO
EtOH, C_6H_6, H_2O
2) $HgCl_2$, HgO
acetone, H_2O
1) *t*-BuOK, DMSO
100 °C
2) $HgCl_2$, HgO
acetone, H_2O
83%
95
OH

Scheme III-21


OTr
PmbO
BnO
PmbO
OH
95
96
$Ph_3P{=}CHSPh$
conditions
TrO
PmbO
OPmb
SPh
OR
OBn
BnBr
97 R = H
98 R = Bn
CONDITIONS
1 NaH, DMSO
2 BuLi, DME, 40 °C, 96
3 BuLi, THF, 0 °C to RT, 96

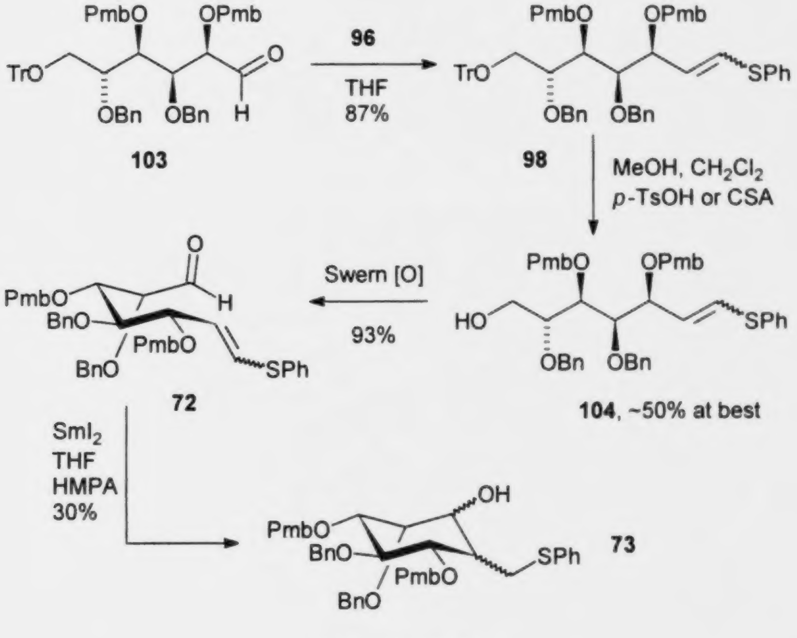
Scheme III-22

Wittig reactions with lactols is a fairly mature field[26] and we envisioned that ylide **96** would react with lactols **95** to give the open chain sugar **97** that could then be benzylated to provide **98** (Scheme III-22). We examined a few conditions for effecting this ring opening, but only the first entry (NaH, DMSO) served to give the target, although in low yield (20%). Attempted trapping of the lactol as its thioketal also did not work, presumably due to the sensitivity of the *p*-methoxybenzyl groups to the Lewis acidic conditions required for thioketalization. A slightly longer but successful and high yielding, route was then examined (Scheme III-23). The lactols were reduced to diol **99** and the primary alcohol was selectively protected as its *t*-butyldimethylsilyl ether **100**. This step was followed by benzylation of *O*-5 and desilylation to afford **102**. Swern oxidation of **102** then provided the pivotal aldehyde **103**. This sequence was highly reproducible and has been carried out on multigram scale with yields comparable to those shown in Scheme III-23.


OTr
PmbO
BnO
O
PmbO
OH
95
LiAlH4
91%
PmbO
OPmb
TrO
OR
OH
OBn
TBSCl
Et3N
DMAP
95%
99 R = H
100 R = TBS
NaH
BnBr
THF
reflux, 98%
PmbO
OPmb
TrO
O
OBn
OBn
H
103
DMSO
(COCl)2
Et3N
CH2Cl2
90%
PmbO
OPmb
TrO
OR
OBn
OBn
TBAF
95%
101 R = TBS
102 R = H

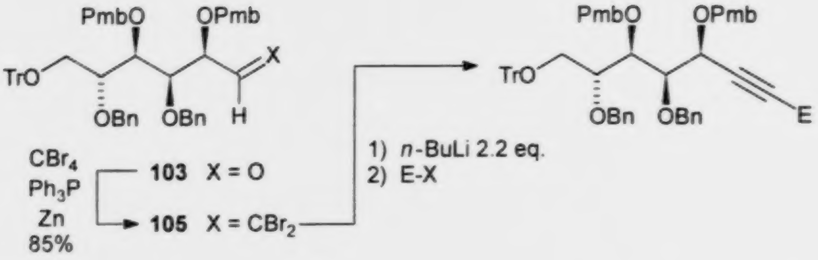
Scheme III-23

Wittig reaction of aldehyde **103** with ylide **96** gave a good yield of **98** as a mixture of isomers. Detritylation proved troublesome as the yields hovered around 50%. Nevertheless, Swern oxidation of **104** finally furnished the radical precursor **72**. Exposure of **72** to standard conditions for ketyl formation (SmI_2, THF, HMPA) as outlined by Curran,[28] gave a 30% (at best) yield of what we presume (^{1}H NMR) to be a mixture of four isomers (**73**) (Scheme III-24).


PmbO
OPmb
TrO
O
OBn
OBn
H
103
96
THF
87%
PmbO
OPmb
TrO
SPh
OBn
OBn
98
MeOH, CH2Cl2
p-TsOH or CSA
O
PmbO
H
BnO
PmbO
BnO
SPh
72
Swern [O]
93%
PmbO
OPmb
HO
SPh
OBn
OBn
104, ~50% at best
SmI2
THF
HMPA
30%
OH
PmbO
BnO
SPh
PmbO
BnO
73

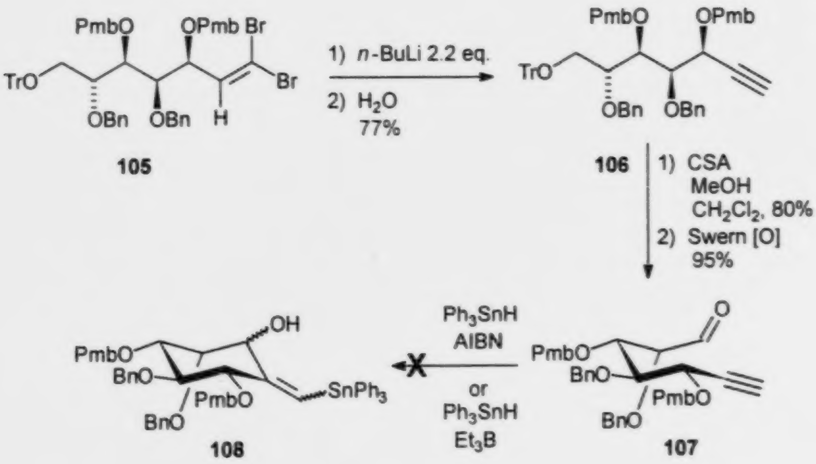
Scheme III-24

Seeing that the yield of this closure could not be improved, we turned our attention to a different route which involved an acetylene function instead of a vinyl sulfide.


PmbO
OPmb
TrO
X
OBn
OBn
H
CBr4
Ph3P
Zn
85%
103 X = O
105 X = CBr2
1) n-BuLi 2.2 eq.
2) E-X
PmbO
OPmb
TrO
OBn
OBn
E

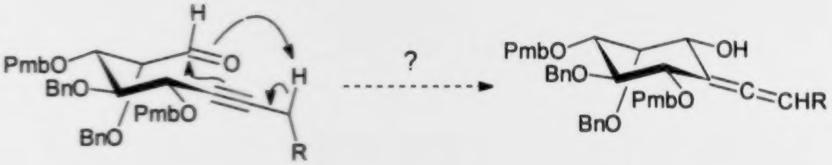
eq. III-3

The generic acetylene (eq. III-3) was available from chemistry developed by Corey,[29] and the advantage of this method is that different groups can be installed on the terminus of the acetylene. We first examined the terminal acetylene **107**, which was made as shown in Scheme III-25. Detritylation of **106** was followed Swern oxidation to furnish **107**. We wished to close the ring by addition of a vinyl radical onto the aldehyde. Exposure to thermal conditions for addition of stannyl radicals to acetylenes gave only complex mixtures; whereas, using the borane method provided only recovered starting material.


PmbO
OPmb Br
TrO
Br
OBn
OBn
H
105
1) n-BuLi 2.2 eq.
2) H2O
77%
PmbO
OPmb
TrO
OBn
OBn
106
1) CSA
MeOH
CH2Cl2, 80%
2) Swern [O]
95%
O
PmbO
BnO
PmbO
BnO
107
Ph3SnH
AIBN
or
Ph3SnH
Et3B
X
OH
PmbO
BnO
PmbO
BnO
SnPh3
108

Scheme III-25

At this point we recognized that an ene reaction may prove very suitable for our needs (eq. III-4) since the hydroxyl function would be introduced at *C*-6 and cleavage of the allene, followed by selective reduction, should provide the target.

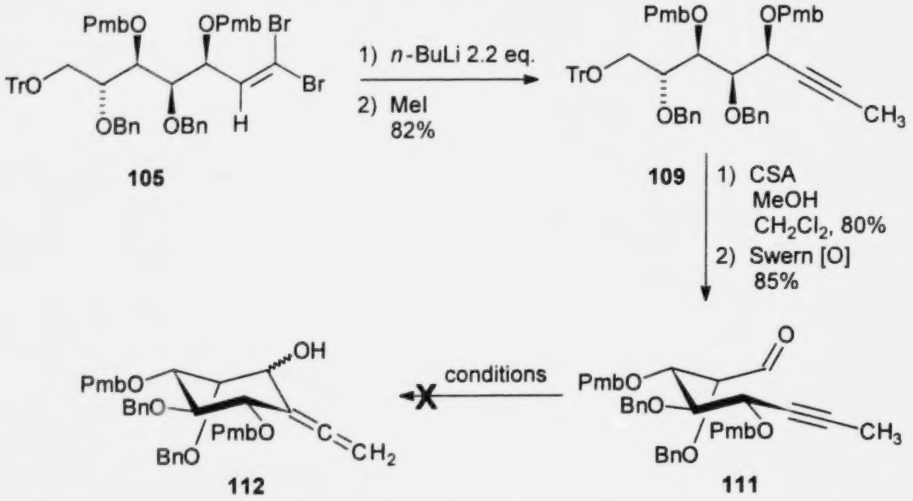


eq. III-4

Although many published examples of intramolecular ene processes exist[30] most of them deal with the reaction of an olefin and aldehyde in the same molecule, and the allylsilane group works quite well in this type of reaction. We wondered what type of group R would best suit our particular needs. We first planned on examining a simple terminal methylene group (R = H) and then a propargyl silane (R = $SiMe_3$). Aldehyde **111** (Scheme III-26), when exposed to various conditions (Table III-1), did not prove to be a satisfactory substrate.

Table III-1 Conditions for Attempted Cyclization of **111**

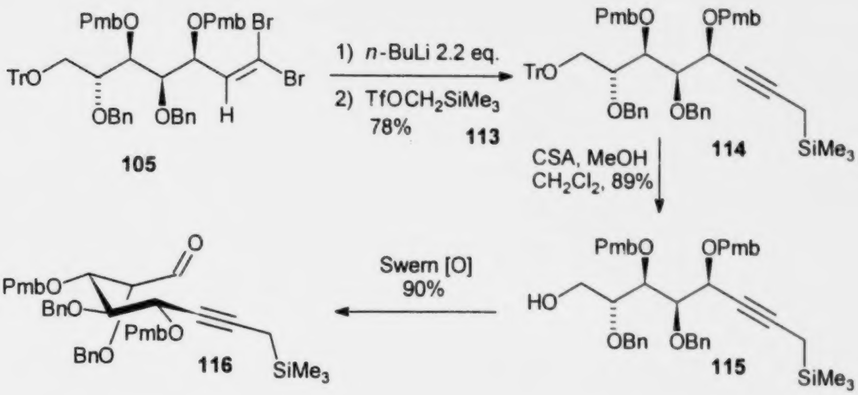
CONDITIONS	RESULT
140 °C, *p*-xylene	not desired product
Me_2AlCl, CH_2Cl_2, -78 °C	21 % isomers
TFA CH_2Cl_2 0 °C	decomposition
TFA $CHCl_3$ RT	decomposition
CSA $CHCl_3$ RT	decomposition
CSA CH_2Cl_2 RT	decomposition



Scheme III-26

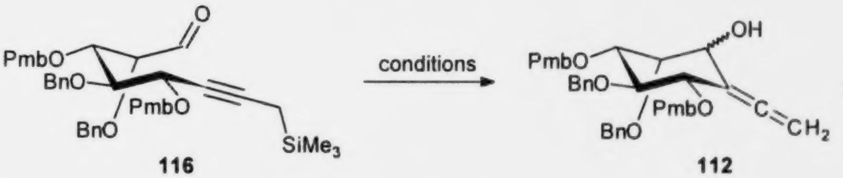
Although the introduction of the methyl group seemed straightforward, numerous attempts were made in order to try and alkylate acetylene **106** via the corresponding lithium acetylide. We subsequently found that only *in situ* alkylation worked well. It was reasoned that the presence of lithium bromide generated in the elimination served to break up problematic aggregates in solution. Presumably, the oxygen atoms chelate the lithium acetylide (either intermolecularly or intramolecularly) thereby making it too sterically encumbered to undergo alkylation with the electrophile. This explanation was borne out by the fact that attempted alkylation of the lithum salt of **106** (made by treatment of acetylene **106** with *n*-BuLi) in THF in the presence of LiBr (2 eq.) gave a 60% yield of **109**, plus recovered acetylene. In the absence of the lithium bromide no alkylation was observed.

The preparation of propargyl silane is shown in Scheme III-27. Alkylation with freshly distilled triflate **113**[31] gave a 78% yield of **114**. Since the purification of **114** proved tedious we found it more convenient to rigorously purifiy the alcohol **115** and not **114**. Swern oxidation of **115** then provided the ene precursor **116**.


1) *n*-BuLi 2.2 eq.
2) TfOCH$_2$SiMe$_3$
78%
113
105
114
CSA, MeOH
CH$_2$Cl$_2$, 89%
Swern [O]
90%
115
116

Scheme III-27

We expected that the reactivity of the propargyl silane would parallel that of the allylsilanes, and that under suitable reaction conditions the silyl group would be lost (or transferred onto oxygen and lost upon work up) to generate the exocyclic allene **112**. Exposure of **116** to various Lewis acids (Table III-2) at low temperature gave only low yields (~20%) of what seemed on the basis of ^{1}H NMR spectroscopy to be the correct product.

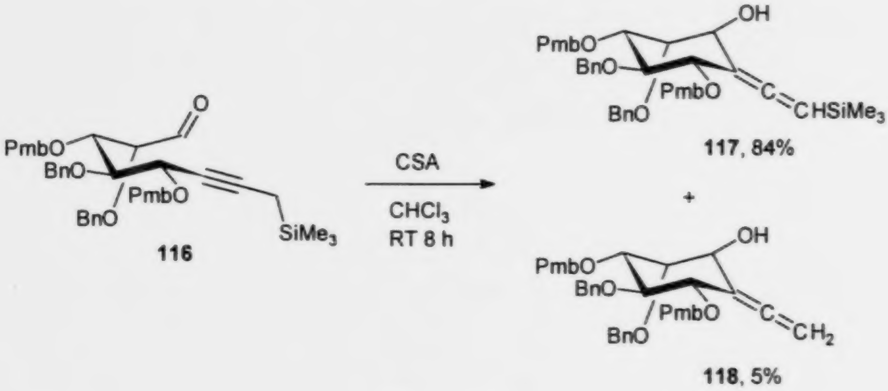

conditions
116
112

eq. III-5

Table III-2 Attempted cyclization of **116**

CONDITIONS	RESULT
TiCl$_4$, CH$_2$Cl$_2$, -78 °C	39%
TBAF, THF, 0 °C	~10%
BF$_3$·OEt$_2$, CH$_2$Cl$_2$, -78 °C	10%, messy
TFA, CH$_2$Cl$_2$ 0 °C	No Reaction

However, we fortuitously stumbled upon the appropriate conditions. A sample of aldehyde **116** was left in a solution of dichloromethane containing a small amount of deuterated chloroform. After standing for two days at room temperature it was found that a new compound had been formed and the structure was deduced as **117**. We were extremely surprised that the silicon unit had been retained. The ideal conditions for cyclization were found to entail conducting the reaction in undistilled aged chloroform in the presence of a catalytic amount of CSA. This gave an **84%** yield of adduct **117** as a **single isomer** in which the configuration of the silicon group and the carbinol carbon were unknown. A second product was also isolated from the reaction mixture and had the structure **118** (Scheme III-28).

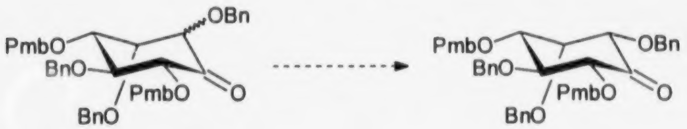


Scheme III-28

When **117** was resubmitted to the initial reaction conditions no desilylated product was formed. This implies that the two products are formed by two different reaction pathways. Reaction of aldehyde in chloroform in the presence of HCl gave a very complex mixture, although some of **118** was formed, as deduced by TLC analysis.

Results from nuclear Overhauser experiments to determine the relative configuration of the newly formed center were not helpful. The 3,5-dinitrobenzoyl derivative of **117** was made, but it proved not to be crystalline.

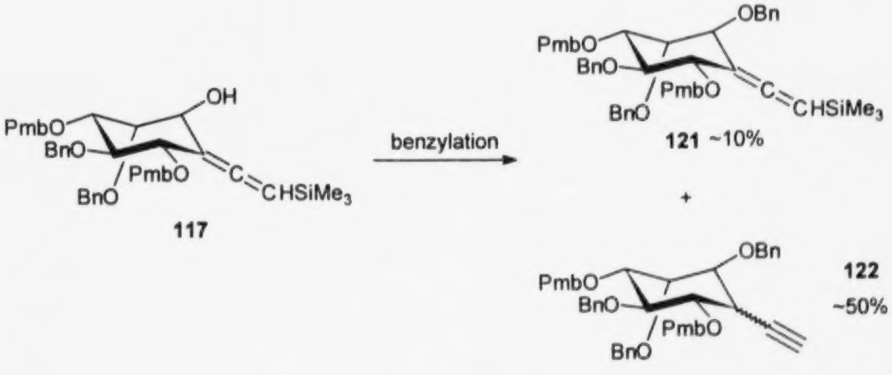
Nevertheless, we decided to carry on the sequence and confirm the configuration of the center in question by conversion to the known benzylated triol **27**. If it proved to be incorrect, we hoped that we could correct it by equilibration of ketone **119** (with the hope that elimination would not be a problem) (eq. III-6).


PmbO
BnO
PmbO
BnO
OBn
O
PmbO
BnO
PmbO
BnO
OBn
O

119 **120**

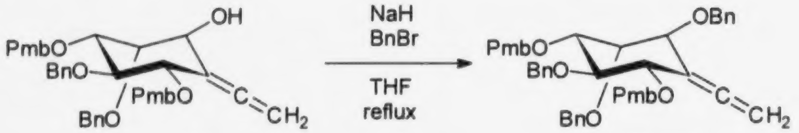
eq. III-6

Benzylation of **117** proved to be difficult. Exposure of **117** to sodium hydride in refluxing THF with either benzyl bromide or benzyl iodide gave the acetylene **122** along with a small amount of the desired **121**.


PmbO
BnO
PmbO
BnO
OH
C
CHSiMe3
117
benzylation
PmbO
BnO
PmbO
BnO
OBn
C
CHSiMe3
121 ~10%
+
PmbO
BnO
PmbO
BnO
OBn
122
~50%

Scheme III-29

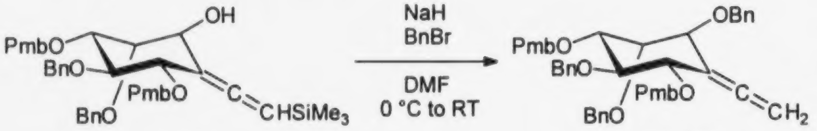
Similar results were encountered using potassium hydride as base. Acidic benzylation, according to the procedure of Bundle and co-workers[32] was not successful, at least in our hands. At this point it became obvious to us that the silicon group was the source of the altered reactivity of **117** towards benzylation and so this group had to be removed.


OH
PmbO
BnO
PmbO
BnO
C
CH2
NaH
BnBr
THF
reflux
OBn
PmbO
BnO
PmbO
BnO
C
CH2

118 **123**, 70% **eq. III-7**

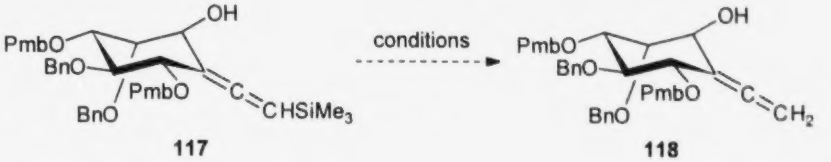
This was clearly the case since benzylation of **118** (NaH, BnBr, THF reflux) proceeded smoothly to give a 70% yield of **123** on a small scale (eq. III-7).

Interestingly enough, benzylation of **117** in DMF using sodium hydride as base with benzyl bromide gave a 50% yield (at best) of desilylated product **123** (eq. III-8), but attempts to improve the yield were not successful.


OH
PmbO
BnO
PmbO
BnO
C
CHSiMe3
NaH
BnBr
DMF
0 °C to RT
OBn
PmbO
BnO
PmbO
BnO
C
CH2

117 **123**, 50% **eq. III-8**

We next examined various acidic conditions (Table III-3) to remove the silicon group (**117**→**118**) by protonolysis (by analogy with vinyl silanes), but none proved to be satisfactory.

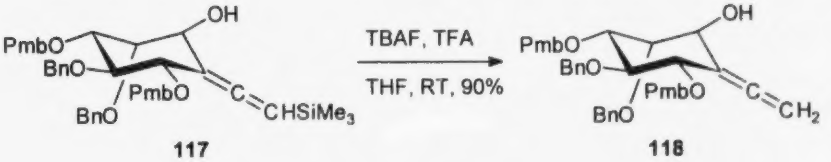


eq. III-8

Table III-3 Attempted Acidic Desilylation of **117**

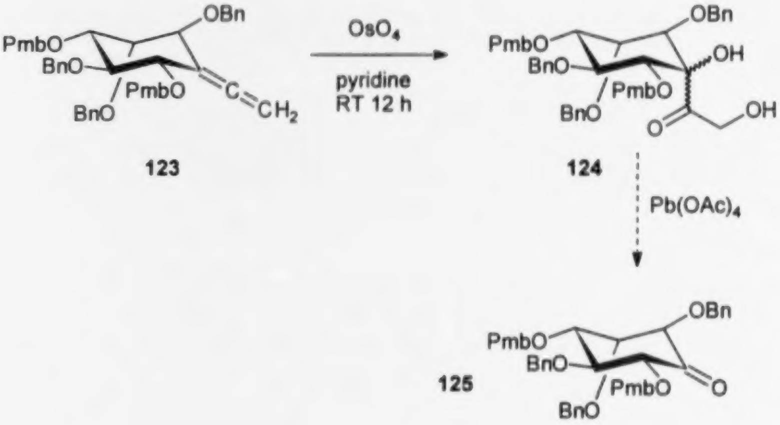
CONDITIONS	RESULT
I_2 cat., PhH, H_2O, reflux	no reaction
I_2, PhH, reflux	messy
TFA (10 eq.), $MeCN/H_2O$	No Reaction
TFA (10eq.), TBAF (4 eq.) $MeCN/H_2O$	No reaction
p-TsOH, $MeCN/H_2O$	No Reaction
p-$TolSO_2H$, $MeCN/H_2O$	No reaction

The results of benzylation in DMF made us wonder if perhaps basic conditions may well serve to remove the silicon group. Treatment of **117** with NaH in MeOH gave only recovered starting material. Reaction with TBAF in THF gave a 64% yield of **118** but, success was finally realized by treating **117** with TBAF in the presence of TFA in THF as solvent to provide a 90% yield of **118** (eq. III-9).



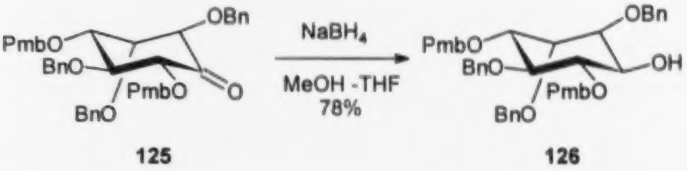
eq. III-9

The oxidative cleavage of the allene function was then examined. Ozonolysis under different conditions (-78°C, or -40°C CH_2Cl_2) of either **121** or **123** gave complex reaction mixtures and this is somewhat in accordance with literature precedent.[33] Epoxidation with *m*-CPBA followed by treatment with acid gave a complex reaction mixture. Osmylation of **123** gave a low (5%) yield of what is presumed to be a mixture of diols **124**. Presumably these diols could be cleaved to the target ketone by cleavage with lead tetraacetate.


PmbO
BnO
PmbO
BnO
OBn
C
CH2
123
OsO4
pyridine
RT 12 h
OH
OH
O
124
Pb(OAc)4
125

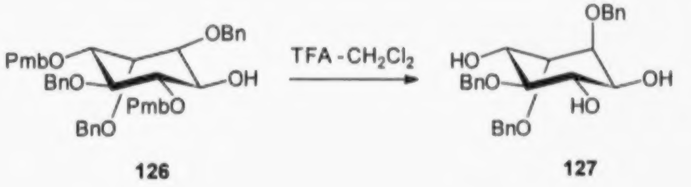
Scheme III-30

It was at this point that the conditions for ozonolysis were re-examined and it was found that addition of pyridine to the reaction mixture gave a 70% yield of ketone **125**. The amount of ozone used was important, since too much ozone did cause decomposition of the substrate probably by oxidation of the benzylic positions in the molecule. Reduction to alcohol **126** was effected by sodium borohydride in methanol/THF to give a 78% yield of the alcohol.


PmbO
BnO
PmbO
BnO
OBn
O
125
NaBH4
MeOH -THF
78%
OH
126

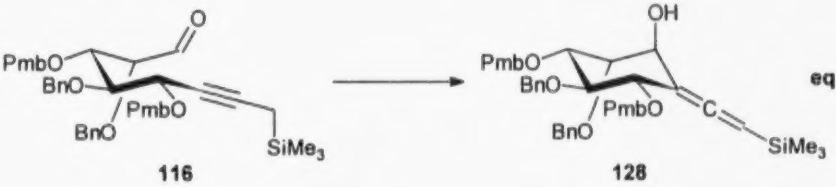
eq. III-10

Tretament of **126** with TFA in dichloromethane at room temperature for 30 min gave a triol that was compared to the literature ^{1}H NMR spectra.[34] The spectra did not match since the signal for H-3 did not have the correct chemical shift. We therfore assume that the compound we have made is actually **127** in whcih the configuration of *O*-3 is axial and not equatorial.


PmbO
BnO
OBn
OH
PmbO
BnO
126
TFA - CH2Cl2
HO
BnO
OBn
OH
HO
BnO
127

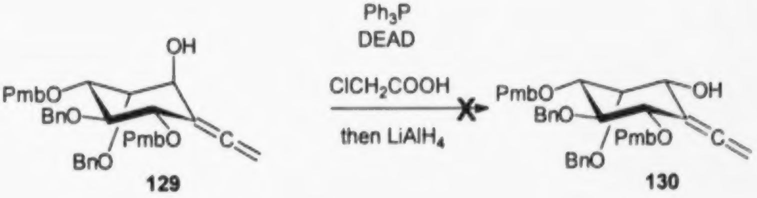
eq. III-11

This means that the ene reaction gave **128**.


O
PmbO
BnO
PmbO
BnO
SiMe3
116
OH
PmbO
BnO
PmbO
BnO
C
SiMe3
128

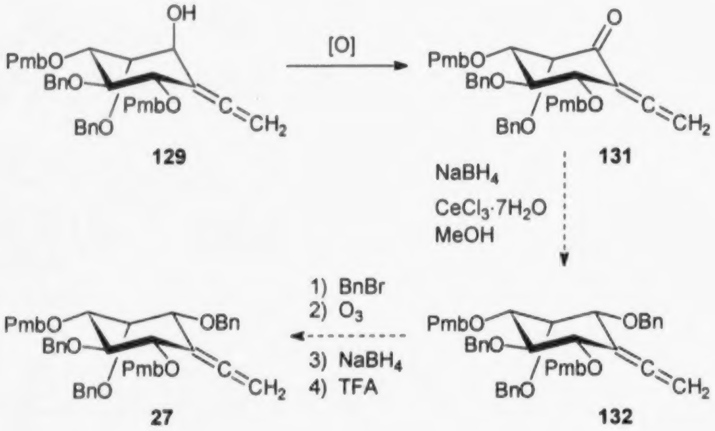
eq. III-12

Attempts to invert the center by Mitsunobu chemistry were not successful. Only a ~10% yield of inverted product was formed along with the product of retention of configuration. This is not surprising since the reaction can go via an S_N1 displacement since an allenic carbonium ion can be formed as an intermediate.


OH
PmbO
BnO
PmbO
BnO
C
129
Ph3P
DEAD
ClCH2COOH
then LiAlH4
PmbO
BnO
OH
PmbO
BnO
C
130

eq. III-13

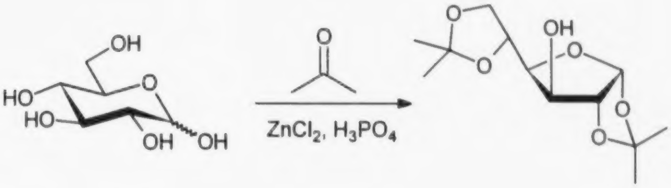
Attempts to oxidize **129** to ketone **131** have so far been unsuccessful (Scheme III-31). If oxidation could be carried out efficiently, then selective reduction should give **132** that could then be further tranformed inot the target triol **27** by a sequence similar to that used above .


OH
PmbO
BnO
PmbO
BnO
C
CH2
129
[O]
O
PmbO
BnO
PmbO
BnO
C
CH2
131
NaBH4
CeCl3·7H2O
MeOH
1) BnBr
2) O3
3) NaBH4
4) TFA
PmbO
BnO
PmbO
BnO
OBn
C
CH2
27
PmbO
BnO
PmbO
BnO
OBn
C
CH2
132

Scheme III-31

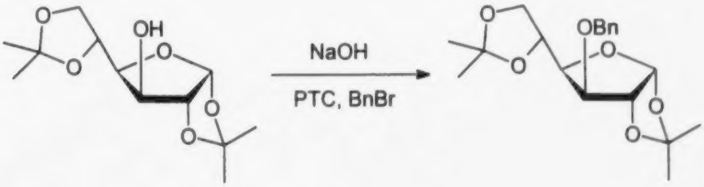
EXPERIMENTAL

1,2:5,6-Diisopropylidene-D-glucofuranose (77).



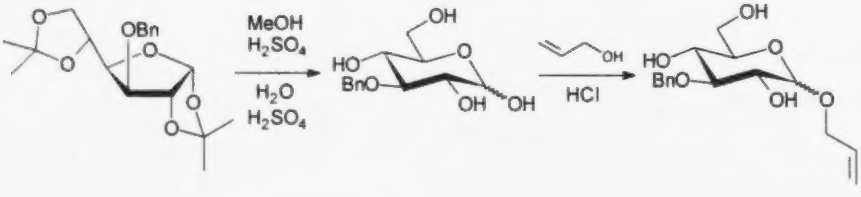
The procedure of Schmidt was followed exactly.[18] Diketal **77** was obtained in 46% yield and had: mp 103-104 °C; $[\alpha]_D = -9.86°$ (c = 0.0071, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 3461 (br), 2987, 2937, 2894, 1457, 1382 cm^{-1}; ^1H NMR (CDCl3, 400 MHz) δ 1.28 (s, 3 H), 1.31 (s, 3 H), 1.39 (s, 3 H), 1.46 (s, 3 H), 2.85 (d, $J = 4$ Hz, 1 H, exchangeable), 3.95 (dd, $J = 6$ Hz, 1 H), 4.01 (dd, $J = 8, 3$ Hz, 1 H), 4.12 (dd, $J = 10, 6.5$ Hz, 1 H), 4.23-4.32 (m, 2 H), 4.48 (d, $J = 4$ Hz, 1 H), 5.89 (d, $J = 4$ Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 25.13 (q'), 26.15 (q'), 26.75 (q'), 26.81 (q'), 67.61 (t'), 73.26 (d'), 74.99 (d'), 81.19 (d'), 85.10 (d'), 105.24 (d'), 109.58 (s'), 111.79 (s'); exact mass, *m/z* calcd for $C_{12}H_{20}O_6$ [$(M-CH_3)^+$] 245.1025, found 245.1026.

3-*O*-Benzyl 1,2:5,6-diisopropylidene-D-glucofuranose (78).[19]



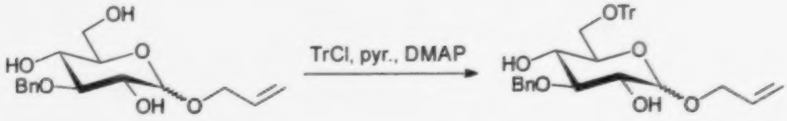
NaOH (41g, 1.02 mol), (*n*-Bu)$_4$NHSO$_4$ (720 mg, 2.12 mmol), and benzyl chloride (24 mL, 0.203 mol) were added sequentially to a stirred solution of **77** (44.08 g, .169 mol) in a mixture of benzene (200 mL) and water (40 mL), and the resulting heterogeneous mixture was refluxed, open to the atmosphere, for 6 h, at which point the reaction was still incomplete (TLC silica, 30% EtOAc-hexane). Benzyl bromide (20 mL, 0.168 mol) was added in one portion and the solution was refluxed for 12 h. The solution was cooled and then poured onto water (100 mL), the organic layer was separated and the aqueous layer was extracted with Et$_2$O (1 x 20 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Distillation of the thick residue gave **78** (46.22 g, 78%) as a pure [^{1}H NMR (400 MHz)], viscous, yellow liquid: bp 155-165°C, 0.17 mm; $[\alpha]_D$ = - 26.97 ° (c = 0.0188, CH$_2$Cl$_2$); FT-IR (CH$_2$Cl$_2$ cast) 2987, 2936, 2892, 1497, 1455, 1381, 1372, 1349 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.30 (s, 3 H), 1.35 (s, 3 H), 1.42 (s, 3 H), 1.48 (s, 3 H), 4.03-4.09 (m, 2 H), 4.13-4.23 (m, 2 H), 4.38-4.45 (m, 1 H), 4.56 (d, *J* = 4 Hz, 1 H), 4.60-4.70 (m, 2 H), 5.86 (d, *J* = 4 Hz, 1 H), 7.30-7.41 (m, 5 H); ^{13}C NMR APT (CDCl$_3$, 75 MHz) δ 25.43 (q'), 26.24 (q'), 26.76 (q'), 26.84 (q'), 67.42 (t'), 72.40 (t'), 72.55 (d'), 81.38 (d'), 81.78 (d'), 82.74 (d'), 105.31 (d'), 108.94 (s'), 111.75 (s'), 127.62 (d'), 127.79 (d'), 128.36 (d'), 137.71 (s'); exact mass, *m/z* calcd for $C_{19}H_{26}O_6$ [(M-CH$_3^+$)$^+$] 335.1495, found 335.1502. Anal. Calcd for $C_{19}H_{26}O_{46}$: C, 65.12; H, 7.34. Found: C, 65.12; H, 7.34.

α,β-Allyl 3-*O*-benzyl-D-glucopyranose (88).



A slightly modified literature procedure[20] was followed for the preparation of 3-*O*-benzyl-D-glucose. 3-*O*-Benzyl 1,2:5,6-diisopropylidene-D-glucofuranose (**78**) (52.7 g, 0.150 mol) was dissolved in a solution of MeOH (110 mL) and H_2SO_4 (53 mL, 1N) and heated to 80°C for 4 h. The solution was then cooled to room temperature, the MeOH was removed in *vacuo*, water (110 mL) was added and heating (80°C) was continued for 1 h. The resulting solution was cooled in an ice bath and neutralized (litmus) with solid $NaHCO_3$. The mixture was evaporated to dryness and the residue was dissolved in hot EtOAc (350 mL), was carefully dried ($MgSO_4$), and filtered hot by gravity using hot EtOAc (200 mL) as a rinse. The solution was carefully evaporated (bumping) and the residue was dried under vacuum (0.5 mm) for 12 h to yield a white solid (39.86 g, 97%) which was not characterized, but used directly in the next step. AcCl (1.2 mL) was added to a solution of the crude tetrol (39.86 g) in freshly distilled allyl alcohol (100 mL). The resulting solution was refluxed for 10 h, cooled to room temperature, and poured into CH_2Cl_2 (150 mL) overlaid with brine (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (6 x 26 cm), using EtOAc-hexane mixtures (40 to 60% EtOAc), gave the allyl glycosides **88** (10.64g, 76% over two steps) as a pure [^{1}H NMR (400 MHz)], beige solid: mp 59-65 °C; $[\alpha]_D = +53.0°$ (c = 0.0217, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3420 (br), 2922, 2880, 1454, 1419 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (t, *J* = 6.5 Hz, 0.5 H, exchangeable), 2.12 (t, *J* = 7 Hz, 0.5 H, exchangeable), 2.19 (d, *J* = 9 Hz, 0.5 H, exchangeable), 2.45 (d, *J* = 2 Hz, 0.25 H, exchangeable), 2.50 (d, *J* = 2.5 Hz, 0.76 H, exchangeable), 3.29-3.42 (m, 0.4 H), 3.71-3.89 (m, 2.2 H), 3.99-4.26 (m, 1.8 H), 4.32-4.39 (m, 0.6 H), 4.70-4.76 (m, 1 H), 4.89 (d, *J* = 4 Hz, 0.7 H), 4.98-5.05 (m, 1 H), 5.21 (d, *J* = 11 Hz, 1.4 H), 5.30 (d, *J* = 18 Hz, 0.5 H), 5.85-5.98 (m, 1 H), 7.25-7.38 (br m, 5 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 62.24 (t'), 62.40 (t'), 68.57 (t'), 70.00 (d'), 70.03 (d'),70.50 (s'), 71.18 (d'), 72.73 (d'), 74.37 (d'), 74.66 (s'), 74.89 (s'), 75.20 (d'), 82.78 (d'), 83.65 (d'), 97.67 (d'), 101.92 (d'), 118.10 (t'), 127.88 (d'), 127.95 (d'), 128.56 (d'), 133.41 (d'), 133.61 (d'), 138.53 (s'). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.09; H, 7.15.

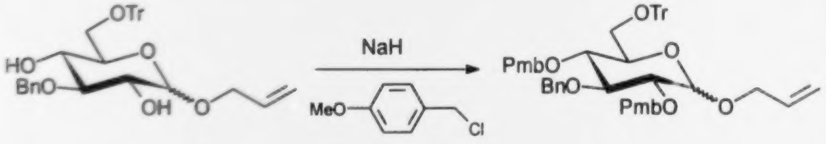
α,β-Allyl 3-*O*-benzyl-1-*O*-trityl-D-glucopyranose (89).



Dry pyridine (130 mL) was added to a dry 250 mL round bottom flask charged with triol **88** (10.32 g, 33.25 mmol), Ph_3CCl (13.91 g, 49.88 mmol), and DMAP (400 mg, 3.27 mmol). The resulting mixture was heated at 110 °C for 8 h, cooled to room temperature, and evaporated. The residue was dissolved in CH_2Cl_2 (200 mL) and washed sequentially with cold (4 °C) aqueous hydrochloric acid (2 x 50 mL, 0.5N), saturated aqueous $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (6 x 24 cm), using EtOAc-hexane mixtures (20 to 30% EtOAc), gave diols **89** (14.62 g, 80%) as a pure [^{1}H NMR (400 MHz)], yellow solid: mp 47-52°C; $[\alpha]_D = + 28.41°$ (c = 0.0145, $CHCl_3$); FT-IR ($CHCl_3$ cast) 3463 (br), 3085, 3060, 3031, 2927, 2878, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (t, *J* = 9 Hz, 0.71 H, exchangeable), 2.34-2.37 (m, 1 H, exchangeable), 2.55 (d, *J* = 2.5 Hz, 0.22 H, exchangeable), 3.28-3.43 (m, 3 H), 3.52-3.80 (m, 3 H), 4.05-4.20 (m, 1 H), 4.25-4.93 (m, 1 H), 4.77-4.85 (t, *J* = 11.5 Hz, 1 H), 4.90-4.98 (m, 2 H), 5.21-5.38 (m, 2 H), 5.90-6.03 (m, 1 H), 7.19-7.52 (br m, 20

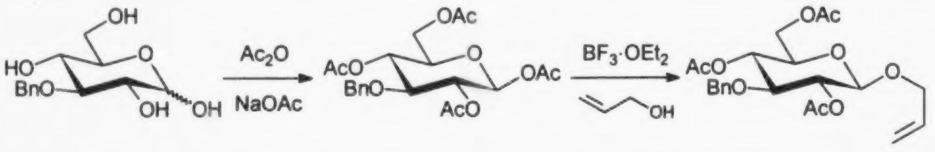
H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 63.77 (t'), 64.00 (t'), 68.32 (t'), 70.00 (t'), 70 39 (d'), 71.30 (d'), 71.41 (d'), 72.47 (d'), 74.12 (d'), 74.27 (d'), 74.69 (t'), 74.96 (t'), 82.85 (d'), 83.90 (d'), 86.80 (s'), 97.33 (d'), 101.59 (d'), 117.92 (t'), 127.02 (d'), 127.79 (d'), 127.90 (d'), 127.95 (d'), 128.45 (d'), 128.61 (d'), 133.66 (d'), 133.80 (d'), 138.60 (s'), 143.67 (d'), 143.75 (s'). Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 75.82; H, 6.64.

α,β-Allyl 3-*O*-benzyl-2,4-di-*O*-*p*-methoxybenzyl-1-*O*-trityl-D-glucopyranose (90).



NaH (2.40 g, 60% dispersion in oil, 60 mmol) was added portionwise to a stirred and cooled (0°C) solution of diols **89** (5.18 g, 9.37 mmol) in THF (80 mL) over 5 min. The resulting mixture was stirred under argon for 30 min, at which point *p*-methoxybenzyl chloride (8.1 mL, 60 mmol) was added neat in one portion by syringe, and stirring was continued at 0°C for 15 min. The cold bath was removed and the solution was allowed to warm to room temperature and then refluxed for 24 h. The mixture was cooled to 0°C and the excess NaH was **carefully** decomposed by addition of MeOH (ca. 10 mL). The mixture was diluted with brine (20 mL) and extracted with Et_2O (3 x 30 mL). The ethereal extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (6 x 24 cm), using EtOAc-hexane mixtures (10 to 20% EtOAc), gave **90** (6.96 g, 94%) as a pure [^{1}H NMR (400 MHz)], off-white solid: mp 41-43.5 °C; $[\alpha]_D$ = +8.8° (c = 0.0207, $CHCl_3$); FT-IR ($CHCl_3$ cast) 3060, 3031, 3005, 2930, 2875, 2835, 1612, 1586, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15-3.25 (m, 1 H), 3.35-3.50 (m, 1 H), 3.55-3.64 (m, 3 H), 3.73-3.85 (m, including singlets at δ 3.75, 3.76. 3.79 and 3.80, 7 H), 3.92-4.00 (m, 0.65 H), 4.06-4.12 (m, 0.38 H), 4.48-4.82 (m, 6 H), 4.89-4.98 (m, 2 H), 5.20-5.46 (m, 2 H), 5.90-6.13 (m, 1 H), 6.66-6.90 (m, 5 H), 7.20-7.39 (br m, 17 H), 7.42-7.55 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 75 MHz) δ 55.23 (q'), 55.25 (q'), 62.46 (t'), 62.62 (t'), 67.96 (t'), 70.06 (d'), 70.50 (d'), 72.80 (t'), 74.64 (t'), 75.92 (t'), 77.62 (d'), 77.90 (d'), 79.91 (d'), 82.24 (d'), 82.31 (d'), 83.33 (d'), 84.78 (d'), 86.32 (s'), 86.35 (s'), 99.25 (d'), 102.77 (d'), 113.62 (d'), 113.83 (d'), 117.34 (t'), 118.22 (t'), 126.79 (d'), 126.94 (d'), 127.54 (d'), 127.63 (d'), 127.78 (d'), 127.96 (d'), 128.08 (d'), 128.25 (d'), 128.41 (d'), 128.85 (d'), 129.20 (d'), 129.59 (d'), 129.78 (d'), 129.86 (d'), 130.12 (s'), 130.18 (s'), 130.50 (s'), 130.78 (s'), 133.94 (d'), 134.25 (d'), 138.24 (t'), 138.74 (t'), 138.92 (t'), 144.00 (s'), 144.26 (s'), 159.15 (s'), 159.20 (s'), 159.27 (s'), 159.35 (s'). Anal. Calcd for $C_{51}H_{52}O_8$: C, 77.25; H, 6.61. Found: C, 77.39; H, 6.56.

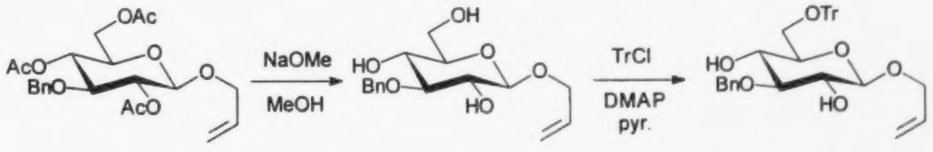
Allyl 2,4,6-tetra-*O*-acetyl -3-*O*-benzyl-β-D-glucopyranoside (92).



The literature procedure[22] for conversion of 3-*O*-benzyl glucose to 1,2,4,6-tetra-*O*-acetyl -3-*O*-benzyl-β-D-glucopyranose was followed using 3-*O*-benzyl glucose (5.34 g, 19.76 mmol), Ac_2O (10 mL), and NaOAc (900 mg). Compound **91** was obtained in 42% (3.67 g) yield. BF_3•OEt_2 (2.20 mL, 16.43 mmol) was added neat over 1 min to a stirred and cooled (0°C) solution of acetate **91** (2.0006 g, 4.56 mmol) and allyl alcohol (0.37 mL, 5.48 mmol) in dry CH_2Cl_2 (15 mL) and crushed

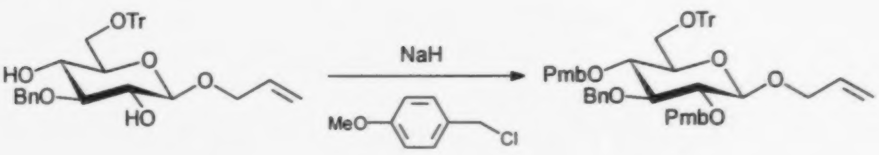
4Å molecular sieves (200 mg). The cold bath was removed and the solution wqas stirred for 1.5 h, and then filtered through Celite (3 x 8 cm). The pad was rinsed with CH_2Cl_2 (50 mL) and the combined filtrates were washed successively with saturated aqueous $NaHCO_3$ (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 x 27 cm,) using 20% EtOAc-hexane, gave **92** (808.4 mg, 41%) as a pure [^{1}H NMR (400 MHz)], beige solid: mp 80-81 °C; $[\alpha]_D = -27.6°$ (c = 0.0183, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 2954, 2937, 2881, 1747, 1454, 1429, 1409, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 6 H), 2.02 (s, 3 H), 2.09 (s, 3 H), 3.56-3.63 (m, 1 H), 3.70 (t, J = 10 Hz, 1 H), 4.04-4.17 (m, 2 H), 4.23 (dd, J = 13, 5 Hz, 1 H), 4.29-4.36 (m, 1 H), 4.46 (d, J = 8 Hz, 1 H), 4.56-4.64 (m, 2 H), 5.05-5.31 (m, 4 H), 5.79-5.90 (m, 1 H), 7.20-7.35 (br m, 5 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 20.74 (q'), 20.82 (q'), 62.28 (t'), 69.59 (d'), 69.73 (t'), 72.00 (d'), 72.45 (d'), 73.71 (t'), 80.03 (d'), 99.75 (d'), 117.37 (t'), 127.76 (d'), 127.79 (d'), 128.40 (d'), 133.48 (d'), 137.75 (s'), 169.17 (s'), 169.31 (s'), 170.75 (s') (I assume that two signals in this spectrum are coincident). Anal. Calcd for $C_{22}H_{28}O_9$: C, 60.54; H, 6.47. Found: C, 60.60; H, 6.63.

Allyl 6-*O*-trityl-3-*O*-benzyl-β-D-glucopyranoside (93).



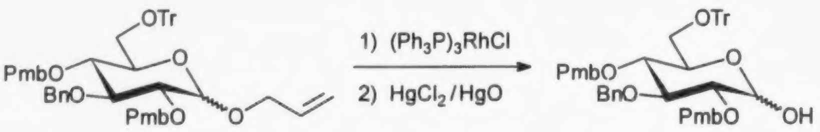
Allyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (**91**) (482.6 mg, 1.555 mmol) was added to stirred solution of NaOMe (200 mg) in dry MeOH (25 mL) and the resulting mixture was stirred for 6 h at room temperature at which point no starting material remained (TLC (silica, 70% EtOAc-hexane). The solution was neutralized with AcOH (litmus), and evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL). The organic solution was washed with brine (1 x 20 mL), dried, and evaporated. The resulting crude triol, DMAP (30 mg, 0.246 mmol), and Ph_3CCl (520 mg, 1.87 mmol) were dissolved in dry pyridine (15 mL) and the mixture was heated at 110°C for 8 h. The solution was then cooled and evaporated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using 13% EtOAc-hexane, gave **93** (746.0 mg, 79% from **91**) as a pure [^{1}H NMR (400 MHz)] white solid: mp 52-54 °C; $[\alpha]_D = -3.56°$ (c = 0.0055, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 3457 (br), 3060, 3031, 2925, 2878, 1490, 1148, 1359 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (d, J = 2 Hz, 1 H, exchangeable), 2.68 (d, J = 2.5 Hz, 1 H, exchangeable), 3.32-3.43 (m, 4 H), 3.55 (dt, J = 9, 2 Hz, 1 H), 3.65 (dt, J = 9, 1 Hz, 1 H), 4.15 (dd, J = 15, 7.5 Hz, 1 H), 4.31-4.42 (m, including triplet at δ 4.33, J = 8 Hz, 2 H), 4.83 (d, J = 12 Hz, 1 H), 4.94 (d, J = 12 Hz, 1 H), 5.23 (dd, J = 11, 1.5 Hz, 1 H), 5.33 (dd, J = 2 , 17.5 Hz, 1 H), 5.91-6.02 (m, 1 H), 7.20-7.41 (m, 14 H), 7.42-7.49 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 64.13 (t'), 70.12 (t'), 71.66 (d'), 74.18 (d'), 74.25 (d'), 74.80 (t'), 83.92 (d'), 86.93 (s'), 101.64 (d'), 118.07 (t'), 127.11 (d'), 127.88 (d'), 128.03 (d'), 128.55 (d'), 128.67 (d'), 133.81 (d'), 138.59 (s'), 143.69 (s'). Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 75.64; H, 6.61.

Allyl 3-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-β-D-glucopyranoside (94).



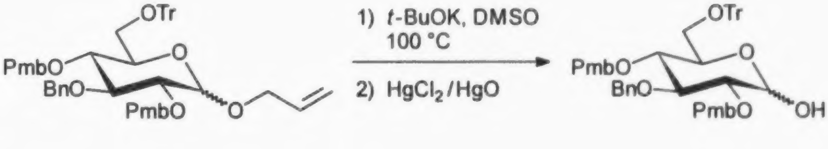
NaH (108.5 mg, 60% dispersion in mineral oil, 2.714 mmol) was added in one portion to a stirred and cooled (0°C) solution of diol **93** (300.0 mg, 0.5428 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 30 min and then *p*-methoxybenzyl chloride (0.37 mL, 2.714 mmol) was added neat in one portion. The cold bath was removed and the solution was allowed to warm to roomt temperature (over ca. 30 min) and was then refluxed for 12 h. The mixture was cooled (0°C), quenched with MeOH (3 mL), diluted with Et_2O (30 mL) and washed with brine (1 x 10 mL). The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined ethereal extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 21 cm), using EtOAc-hexane mixtures (10 to 20% EtOAc), gave **94** (326.1 mg, 76%) as a pure [^{1}H NMR (400 MHz)], white solid: mp 42-44 °C; $[\alpha]_D$ = - 4.27° (c = 0.0157, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3088, 3060, 3032, 3001, 2931, 2876, 2835, 1612, 1586, 1513, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22 (dd, *J* = 11, 4 Hz, 1 H), 3.35-3.40 (m, 1 H), 3.52-3.59 (m, 3 H), 3.22-3.31 (m, including singlet at δ 3.76 and 3.80, 7 H), 4.20-4.30 (m, including doublet of triplets at δ 4.23, *J* = 6.5, 2 Hz, 2 H), 4.45-4.55 (m, 2 H), 4.60 (d, *J* = 9.5 Hz, 1 H), 4.70 (d, *J* = 11 Hz, 1 H), 4.79 (d, *J* = 11 Hz, 1 H), 4.89 (d, *J* = 12.5 Hz, 1 H), 4.92 (dq, *J* = 11, 1.5 Hz, 1 H), 5.25 (d, *J* = 12 Hz, 1 H), 5.41 (dq, *J* = 17.5, 2 Hz, 1 H), 6.00-6.12 (m, 1 H), 6.65-6.76 (m, 4 H), 6.81-6.88 (m, 2H), 7.20-7.35 (br m, 16 H), 7.48-7.55 (m, 5 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.15 (q', we assume two signals are coincident at 55.15), 62.37 (t'), 69.98 (t'), 74.53 (t'), 75.83 (t'), 77.53 (d', we assume two signals are coincident 77.53), 82.15 (d'), 84.70 (d'), 86.29 (s'), 102.71 (d'), 113.55 (d'), 113.74 (d'), 117.28 (t'), 126.90 (d'), 127.58 (d'), 127.74 (d'), 127.89 (d'), 128.35 (d'), 128.61 (d'), 129.80 (d'), 130.04 (s'), 130.70 (d'), 134.18 (d'), 138.66 (s'), 143.90 (s'), 159.13 (s'), 159.19 (s'). Anal. Calcd for $C_{51}H_{52}O_8$: C, 77.25; H, 6.61. Found: C, 77.28; H, 6.51.

3-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl--D-glucopyranose (95).



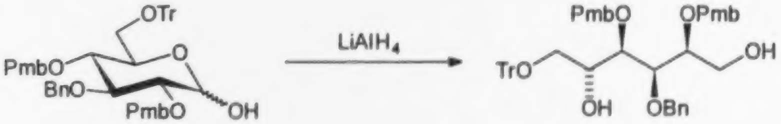
$Rh(PPh_3)_3Cl$ (800.0 mg, 0.8464 mmol)[23] and DABCO (398.0 mg, 3.55 mmol) were added sequentially to a stirred solution of **91** (3.75 g, 4.73 mmol) in a mixture of benzene (45 mL), EtOH (105 mL, 98%), and water (15 mL). The resulting mixture was stirred at room temperature for 1 h and then refluxed, open to the atmosphere, for 36 h. The resulting brown solution was evaporated and the residue dissolved in 9:1 acetone:water (150 mL). $HgCl_2$ (14,4 g, 53.04 mmol) and HgO yellow (40 mg, 0.185 mmol) were added and the resulting mixture was stirred at room temperature for 12 h.[24] The mixture was evaporated, diluted with CH_2Cl_2 (100 mL), and filtered through a pad of Celite (6 x 6 cm). The pad was rinsed with CH_2Cl_2 (200 mL) and the combined filtrates were washed with 20% aqueous NaI (1 x 60 mL). The aqueous layer was extracted with CH_2Cl_2 (1 x 40 mL) and the combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (4 x 31 cm), using EtOAc-hexane mixtures (15 to 30% EtOAc), gave **95** (3.27 g, 92%) as a pure [^{1}H NMR (400 MHz)] solid: mp 58-64 °C; $[\alpha]_D = +7.8°$ (c = 0.0032, $CHCl_3$); FT-IR ($CDCl_3$ cast) 3428 (br), 3060, 3031, 3006, 2932, 2877, 2835, 1612, 1586, 1513, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85 (d, J = 2.5 Hz, 0.56 H, exchangeable), 3.02 (d, J = 6 Hz, 0.16 H, exchangeable), 3.16-3.25 (m, 0.87 H), 3.40-3.49 (m, 0.56 H), 3.52-3.69 (m, 1.86 H), 3.70-3.83 (m, including singlet at δ 3.76, 3.79, and 3.80, 7.71 H), 3.87 (t, J = 4 Hz, 0.70 H), 3.99-4.03 (m, 0.61 H), 4.25 (d, J = 10 Hz, 0.93 H), 4.60 (dd, J = 11, 2 Hz, 0.90 H), 4.65-4.92 (m, 4.40 H), 5.29-5.33 (br m, 0.51 H), 6.65-6.71 (m, 2 H), 6.72-6.76 (m, 2 H), 6.82-6.90 (m, 2H), 7.19-7.39 (br m, 16 H), 7.93-7.51 (m, 6 H); ^{13}C NMR APT (CDCl$_3$, 100.6 MHz) δ 55.25 (q'), 55.28 (q'), 62.26 (t'), 62.56 (t'), 70.59 (d'), 72.96 (t'), 74.56 (t'), 74.96 (d'), 75.92 (t'), 77.50 (d'), 80.14 (d'), 81.89 (d'), 83.13 (d'), 84.70 (d'), 86.31 (s'), 86.50 (s'), 91.30 (d'), 97.65 (d'), 113.59 (d'), 113.86 (d'),113.95 (d'), 126.94 (d'), 126.98 (d'), 127.70 (d'), 127.81 (d'), 127.93 (d'), 128.08 (d'), 128.45 (d'), 128.65 (d'), 128.86 (d'), 129.63 (d'), 129.72 (d'), 129.79 (d'), 130.11 (s'),130.25 (s'), 130.63 (s'), 138.62 (s'), 138.73 (s'), 143.85 (s'), 143.94 (s'), 159.12 (s'), 159.14, (s'). An analytical sample was prepared by flash chromatography over silica gel, using 10% EtOAc-hexane. Anal. Calcd for C$_{48}$H$_{48}$O$_8$: C, 76.57; H, 6.42. Found: C, 76.18; H, 6.41. The same reaction with allyl 3-*O*-benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-β-D-glucopyranoside gave a product identical with that obtained from the reaction with α, β-Allyl 3-*O*-benzyl-2,4-di-*O*-*p*-methoxybenzyl-1-*O*-trityl-D-gluco-pyranose (**94**).

3-*O*-benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-D-glucopyranose (95).



DMSO (10 mL) was added in one portion to a suspension of **90** (4.172 g, 5.261 mmol) and *t*-BuOK (590.0 mg, 5.261 mmol).[25] The mixture was stirred to dissolve the solids and then heated at 100°C for 15 min at which point no starting material remained (TLC (silica, 30% EtOAc). The solution was allowed to cool to room temperature and then poured into water (100 mL) and the orange mixture was extracted with Et$_2$O (4 x 40 mL). The ethereal extracts were washed with water (1 x 30 mL), and brine (1 x 30 mL), dried, and evaporated. The solid residue was dissolved in 8:1 acetone:water (20 mL) and HgO (1.71 g, 7.89 mmol) was added to the resulting solution (stirring). A solution of $HgCl_2$ (2.143 g, 7.89 mmol) in 8:1 acetone:water (7mL plus 2 mL as a rinse) was added dropwise and stirring was continued for 2 h at room temperature. The mixture was filtered through a pad of Celite (5 x 3 cm) and the pad was rinsed with acetone (50 mL). The combined filtrates were evaporated and the residue was dissolved in Et_2O (70 mL), washed with 20% aqueoue NaI (1 x 40 mL), and brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 15% EtOAc-hexane, gave **95** (3.27 g, 83%) as a pure [^{1}H NMR (400 MHz)], off-white solid that was spectroscopically identical to that obtained in the previous experiment.

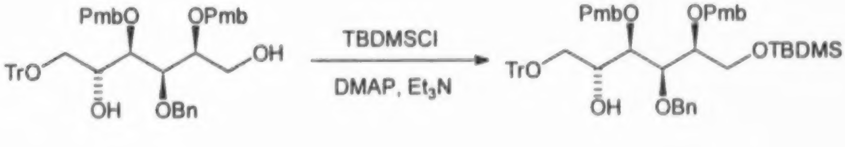
3-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-D-glucitol (99).



$LiAlH_4$ (35 mg, 0.9223 mmol) was added in three portions to a stirred and cooled (0°C) solution of **95** (285.2 mg, 0.3758 mmol) in THF (8 mL). The cold bath was removed and the resulting solution was stirred for 1 h. The solution was cooled to 0°C, and water (0.035 mL), 15% (w/v) NaOH (0.035 mL), and water (0.105 mL) were added sequentially . The cold bath was removed and the solution was stirred for 30 min and then filtered through a pad of Celite (1.5 x 6 cm). The pad was rinsed with Et_2O (50 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2.5 x 23 cm), using EtOAc-hexane mixtures (25 to 40% EtOAc), gave **99** (259.9, mg, 91%) as a pure [^{1}H NMR (400 MHz)], white solid: mp 41-42 °C; $[\alpha]_D = - 6.78°$ (c = 0.0115, $CHCl_3$); FT-IR ($CHCl_3$

cast) 3460 (br), 2933, 2909, 2877, 2835, 1612, 1513, 1491, 1463, 1449, 1302 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (t, *J* = 7.5 Hz, 1 H, exchangeable), 3.11 (m, 1H, exchangeable), 3.25 (dd, *J* = 9.5, 5 Hz, 1 H), 3.32 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.51 (m, 1 H), 3.68 (m, 1 H), 3.72-3.79 (m, including singlet at δ 3.71 and 3.72, 7 H), 3.82 (dd, *J* = 7, 1 Hz, 1 H), 4.29-4.35 (m, including doublet at δ 4.32, *J* = 4.5 Hz, 2 H), 4.46-4.56 (m, 3 H), 4.64 (d, *J* = 12 Hz, 1 H), 6.71-6.78 (m, 2 H), 6.79-6.85 (m, 2 H), 7.15-7.30 (br m, 16 H), 7.37-7.96 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.23 (q', we assume two signals are coincident at 55.23), 61.85 (t'), 64.69 (t'), 70.75 (d'), 72.46 (t'), 72.66 (t'), 74.33 (t'), 76.43 (d'), 79.05 (d'), 79.32 (d'), 86.63 (s'), 113.72 (d'), 113.87 (d'), 127.08 (d'), 127.86 (d'), 128.37 (d'), 128.44 (d'), 128.57 (d'), 128.76 (d'), 129.61 (d'), 129.74 (d'), 129.90 (s'), 130.29 (s'), 137.84 (s'), 143.85 (s'), 159.30 (s', we assume two signals are coincident at 159.30). Anal. Calcd for $C_{48}H_{50}O_8$: C, 76.37; H, 6.68. Found: C, 76.15; H, 6.83.

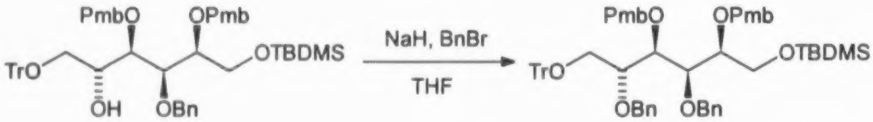
3-*O*-Benzyl-1-*O*-*t*-butyldimethylsilyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-D-glucitol (100).



A general procedure[27] was followed with slight modifications. Et_3N (0.27 mL, 1.9 mmol) was added via syringe in one portion to a stirred solution of diol **99** (955.6 mg, 1.266 mmol), DMAP (37.0 mg, 0.306 mmol), and *t*-$BuMe_2SiCl$ (286.0 mg, 1.899 mmol) in CH_2Cl_2 (30 mL). The resulting solution was stirred for 16 h at room temperature, diluted with CH_2Cl_2 (50 mL) and washed with brine (2 x 20 mL). The organic extracts were dried and evaporated. Flash chromatography of the residue

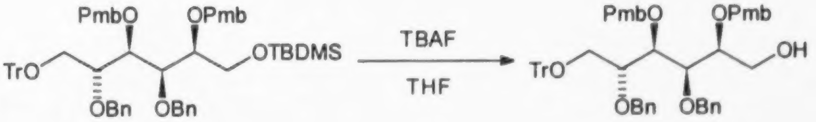
over silica gel (2.5 x 24 cm), using 8% EtOAc-hexane gave, **100** (1.0451 g, 95%) as a pure [^{1}H NMR (400 MHz)], gummy solid: $[\alpha]_D = +3.93°$ (c = 0.0150, $CHCl_3$); FT-IR ($CDCl_3$ cast) 3510 (br), 3086, 3060, 3032, 3001, 2952, 2929, 2882, 2856, 2836, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6 H), 0.90 (s, 9 H), 3,13 (d, J = 5 Hz, 1 H, exchangeable), 3.30 (dd, J = 10, 5.5 Hz, 1 H), 3.35 (dd, J = 10. 3.5 Hz, 1 H), 3.67-3.87 (br m, including singlet at δ 3.80 and 3.81, 11 H), 3.99-4.06 (m, 1 H), 4.36 (q, J = 11 Hz, 2 H), 4.54-4.69 (m, 4 H), 6.75-6.80 (m, 2 H), 6.83-6.89 (m, 2 H), 6.99-7.03 (m ,2 H), 7.20-7.35 (br m, 16 H), 7.45-7.52 (m, 6H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -3.63 (q'), 18.16 (s'), 25.60 (q'), 55.19 (q', we assume two signals are coincident at 55.19), 63.06 (t'), 64.89 (t'), 71.14 (d', we assume two signals are coincident at 71.14), 72.48 (t'), 72.79 (t'), 73.95 (t'), 78.25 (d'), 79.30 (d'), 86.52 (s'), 113.54 (d'), 113.64 (d'), 126.94 (d'), 127.63 (d'), 127.76 (d'), 128.25 (d'), 128.32 (d'), 128.79 (d'), 129.58 (d'), 129.71 (d'), 130.24 (s'), 130.66 (s'), 138.09 (s'), 143.96 (s'), 159.07 (s', we assume two signals are coincident at 159.07). Anal. Calcd for $C_{54}H_{64}O_8Si$: C, 73.24; H, 7.42. Found: C, 73.32; H, 7.40.

3,5-di-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-1-*O*-*t*-butyldimethylsilyl-6-*O*-trityl-D-glucitol (101).



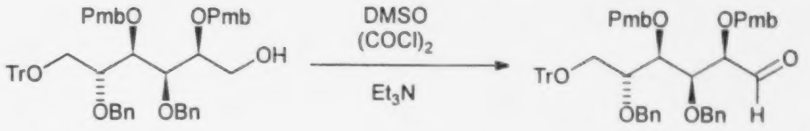
NaH (100 mg, 60% dispersion in mineral oil, 2.50 mmol) was added in three portions to stirred and cooled (0°C) solution of alcohol **100** (1.0058 g, 1.157 mmol) in THF (30 mL). The resulting mixture was stirred for 30 min and then benzyl bromide (0.30 mL, 2.5 mmol) was added neat in one portion by syringe. The cold bath was removed and the mixture was stirred for 1 h and then refluxed for 14 h. The resulting milky white mixture was cooled (0°C) and quenched with MeOH (3 mL), diluted with brine (10 mL), and extracted with Et_2O (3 x 30 mL). The ethereal extracts were washed with brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using EtOAc-hexane mixtures (5 to 20% EtOAc), gave **101** (1.0864 g, 98%) as a pure [^{1}H NMR (400 MHz)], thick syrup: $[\alpha]_D = +5.71°$ (c = 0.0238, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 3061, 3031, 2952, 2927, 2882, 2854, 1612, 1585, 1513, 1492 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ -0.02 (d, J = 2.5 Hz, 6 H), 0.86 (s, 9 H), 3.37 (dd, J = 10.5, 5.5 Hz, 1 H), 3.56 (dd, J = 11, 3 Hz, 1 H), 3.60-3.70 (m, 3 H), 3.71-3.80 (m, including singlet at δ 3.73 and 3.78, 8 H), 4.02 (t, J = 6 Hz, 1 H), 4.39 (d, J = 12.5 Hz, 1 H), 4.48-4.75 (m, 8 H), 6.68-6.72 (m, 2 H), 6.73-6.79 (m, 2 H), 6.92-6.97 (m, 2 H), 7.15-7.32 (br m, 21 H), 7.43-7.49 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -5.40 (q'), 18.22 (s'), 25.98 (q'), 55.23 (q', we assume two signals are coincident at 55.23), 62.23 (t'), 63.88 (t'), 72.16 (t'), 72.76 (t'), 73.48 (t'), 74.45 (t'), 78.26 (d'), 78.58 (d'), 79.65 (d'), 80.24 (d'), 86.77 (s'), 113.45 (d'), 113.62 (d'), 126.91 (d'), 127.29 (d'), 127.77 (d', we assume two signals are coincident at 127.77), 128.14 (d'), 128.22 (d', we assume two signals are coincident at 128.22), 128.88 (d', we assume two signals are coincident at 128.88), 129.52 (d'), 129.66 (d'), 103.93 (s'), 131.11 (s'), 138.84 (s'), 144.12 (s'), 158.91 (s'), 159.01 (s'). Anal. Calcd for $C_{61}H_{70}O_8Si$: C, 76.38; H, 7.36. Found: C, 76.50; H, 7.51.

3,5-di-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-D-glucitol (102).



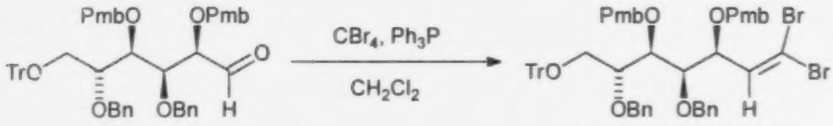
TBAF (5.30 mL, 1M in THF, 5.30 mmol) was added in one portion via syringe to a stirred solution of **101** (5.01 g, 5.22 mmol) in THF (100 mL). The resulting solution was stirred for 4 h at room temperature, diluted with Et_2O (50 mL), and washed with water (1 x 50 mL). The aqueous layer was extracted with ether (2 x 30 mL) and the combined organic extracts were washed with brine (1 x 50 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (5 x 33 cm), using EtOAc-hexane mixtures (20 to 40% EtOAc), gave **102** (5.21 mg, 95%) as a pure [^{1}H NMR (400 MHz)], white solid: mp 36.5-39 °C; $[\alpha]_D$ = - 11.92° (c = 0.0266 CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3476 (br), 3060, 3031, 3002, 2933, 2910, 2875, 2835, 1612, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (br t, *J* = 6 Hz, 1 H, exchangeable), 3.43 (dd, *J* = 11, 5.5 Hz, 1 H), 3.52-3.61 (m, 2 H), 3.61-3.88 (br m, including singlet at δ 3.75 and 3.78, 12 H), 4.04 (t, *J* = 6 Hz, 1 H), 4.41 (d, *J* = 12 Hz, 1 H), 4.46-4.55 (m, 4 H), 4.61 (s, 2 H), 4.75 (d, *J* = 12 Hz, 1 H), 6.75 (d, *J* = 12 Hz, 2 H), 6.81 (d, *J* = 9 Hz, 2 H), 7.00 (d, *J* = 9 Hz, 2 H), 7.16-7.36 (m, 21 H), 7.45-7.52 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.21 (q', we assume two signals are coincident at 55.21), 61.93 (t'), 63.18 (t'), 72.19 (t', we assume two signals are coincident at 72.19), 73.29 (t'), 74.39 (t'), 78.04 (d'), 78.76 (d'), 79.12 (d'), 79.26 (d'), 86.90 (s'), 113.54 (d'), 113.81 (d'), 126.95 (d'), 127.36 (d'), 127.58 (d'), 127.78 (d', we assume two signals are coincident at 127.78), 128.15 (d'), 128.29 (d'), 128.83 (d'), 129.57 (d'), 129.68 (d'), 130.40 (s'), 130.52 (s'), 138.40 (s'), 138.67 (s'), 144.01 (s'), 159.05 (s'), 159.24 (s'). Anal. Calcd for $C_{55}H_{56}O_8$: C, 78.17; H, 6.68. Found: C, 78.14; H, 6.74.

3,5-di-*O*-Benzyl-2,4-di-*O*-*p*-methoxybenzyl-6-*O*-trityl-D-glucose (103).



DMSO (0.84 mL, 11.84 mmol) was added dropwise to a stirred and cooled (-78°C) solution of $(COCl)_2$ (0.77 mL, 8.877 mmol) in CH_2Cl_2 (40 mL). The resulting solution was stirred at -78°C for 20 min, at which point a solution of **102** (2.5003 g, 2.959 mmol) in CH_2Cl_2 (10 mL plus 3 mL as a rinse) was added via cannula over 1 min. The solution was stirred for 30 min at -78°C then Et_3N (4.12 mL, 24.59 mmol) was added dropwise over ca. 2 min. The cold bath was removed and the solution was allowed to warm to ambient temperature over ca. 6 h. The solution was diluted with water (2 mL) and CH_2Cl_2 (50 mL) and washed with brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (5 x 27 cm), using EtOAc-hexane mixtures (7 to 20% EtOAc), gave **103** (2.2376 g, 90%) as a pure [^{1}H NMR (400 MHz)], white solid: mp 46-48 °C; $[\alpha]_D = + 1.67°$ (c = 0.0150, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 3086, 3060, 3031, 3003, 2932, 2871, 2835, 1727, 1612, 1585, 1513, 1492 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.38 (dd, J = 11, 5 Hz, 1 H), 3.75 (dd, J = 10, 3 Hz, 1 H), 3.78-3.89 (m, including singlet at δ 3.82 and 3,84, 7 H), 3.91 (d, J = 5.5 Hz, 1 H), 4.12-4.20 (m, 2 H), 4.33 (d, J = 11 Hz, 1 H), 4.36-4.54 (m, 4 H), 4.59 (d, J = 12 Hz, 1 H), 4.81 (dd, J = 22, 12 Hz, 1 H), 6.70-6.75 (m, 2 H), 6.80-6.93 (m, 4 H), 7.13-7.20 (m, 2 H), 7.21-7.32 (m, 14 H), 7.33-7.46 (m, 5 H), 7.48-7.56 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.21 (q'), 55.26 (q'), 62.62 (t'), 72.16 (t'), 72.75 (t'), 73.03 (t'), 73.92 (t'), 76.46 (d'), 78.70 (d'), 80.01 (d'), 80.67 (d'), 86.81 (s'), 113.39 (d'), 113.89 (d'), 127.00 (d'), 127.21 (d'), 127.43 (d'), 127.84 (d'), 128.13 (d'), 128.36 (d'), 128.85 (d'), 129.52 (s'), 129.72 (d'), 129.97 (s'), 130.20 (d'), 137.67 (s'), 138.60 (s'), 143.96 (s'), 158.98 (s'), 159.46 (s'), 201.03 (d'). Anal. Calcd for $C_{55}H_{54}O_8$: C, 78.36; H, 6.46. Found: C, 78.01; H, 6.52.

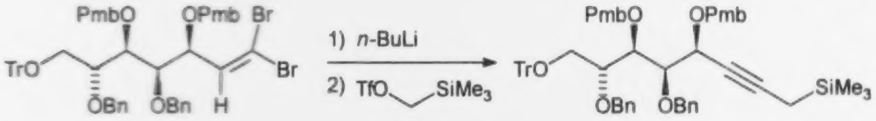
1,1-Dibromo-1,2-dideoxy-4,6-di-*O*-benzyl-3,5-di-*O*-*p*-methoxybenzyl-7-*O*-trityl-D-*gluco*-1-heptenitol (105).[29]



CH_2Cl_2 (40 mL) was added to a suspension of Zn dust (353.3 mg, 5.4060 mmol), Ph_3P (1.4180 g, 5.4060 mmol), and CBr_4 (1.7929 g, 5.4060 mmol) and the resulting mixture was tirred for 26 h at room temperature, at which point the solution had attained a maroon color. A solution of aldehyde **103**(1.1393 g, 1.352 mmol) in CH_2Cl_2 (10 mL plus 3 mL as a rinse) was added via cannula in one portion. The resulting solution was stirred for 15 min and then poured into CH_2Cl_2 (50 mL) overlaid with saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were was washed with brine (1 x 40 mL), dried, and filtered through a pad of silica (5 x 2 cm). The pad was washed with CH_2Cl_2 (80 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (3.5 x 22 cm), using EtOAc-hexane mixtures (8 to 12% EtOAc), gave **105** (1.2141 g, 90%) as a pure [^{1}H NMR (400 MHz)], white gummy solid:$[\alpha]_D = +17.1°$ (c = 0.0152, $CHCl_3$); FT-IR ($CDCl_3$ cast) 3060, 3031, 2932, 2909, 2871, 2835, 1612, 1585, 1513, 1492 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39-3.48 (m, 2 H), 3.68-3.78 (m, including doublet at δ 3.76, 5 H), 3.79 (s, 3 H), 4.09 (t, J = 6 Hz, 1 H), 4.23 (dd, J = 9, 5 Hz, 1 H), 4.33 (d, J = 11 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 4.50-4.68 (m, 5 H), 4.72 (d, J = 12 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 6.74 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 9 Hz, 2 H), 6.99 (d, J = 9 Hz, 2 H), 7.15-7.36 (br m, 21 H), 7.42-7.52 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.18 (q', we assume two signals are coincident at

55.18), 63.08 (t'), 70.88 (t'), 72.36 (t'), 73.87 (t'), 74.41 (t'), 78.47 (d'),78.94 (d'), 79.51 (d'), 79.68 (d'), 86.66 (s'), 92.27 (s'), 113.45 (d'), 113.76 (d'), 126.88 (d'), 127.33 (d'), 127.52 (d'), 127.74 (d'), 128.20 (d'), 128.25 (d'), 128.87 (d'), 129.59 (s'), 129.68 (d'), 129.82 (d'), 130.76 (s'), 137.51 (d'), 138.28 (s'), 138.71 (s'), 143.99 (s'), 158.92 (s'), 159.30 (s'), two signals in this spectrum are missing or coincident. Anal. Calcd for $C_{56}H_{54}O_7Br_2$: C, 67.34; H, 5.45. Found: C, 67.40; H, 5.41.

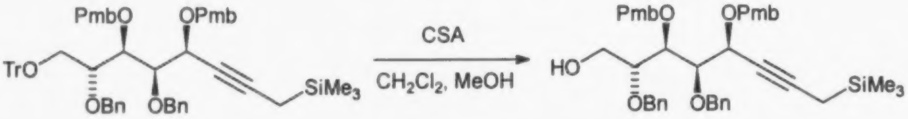
4,6-di-*O*-benzyl-1,2-dideoxy-3,5-di-*O*-*p*-methoxybenzyl-1-methyltrimethylsilyl-7-*O*-trityl-D-*gluco*-1-heptynitol (114).



n-BuLi (0.37 mL, 1.6M in hexane, 0.5933 mmol) was added over 30 sec to a stirred and cooled (-78°C) solution of dibromide **105** (267.6 mg, 0.2679 mmol) in THF (15 mL). The resulting solution was stirred at -78°C for 1 h, at which point the cold bath was removed and stirring was continued for 1.5 h. Freshly prepared $Me_3SiOSO_2CF_3$[31] (114.0 uL, 0.6698 mmol) was then added in one portion by syringe and the solution was stirred for 1.5 h at room tempertaure, diluted with Et_2O (30 mL) and washed with brine (1 x 10 mL). The aqueous layer was extracted with ether (2 x 20 mL) and the combined ethereal extracts dried and evaporated. Flash chromatography of the residue over silica gel (3 x 28 cm), using EtOAc-hexane mixtures (5 to 30% EtOAc), gave **114** (220.3 mg, 89%) as a pure [^1H NMR (400 MHz)], gummy solid: $[\alpha]_D = + 17.67°$ (c = 0.0129, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3061, 3031, 3002, 2953, 2933, 2909, 2874, 2835, 2212, 1612, 1586, 1514, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.15 (s, 9 H), 1.64 (dd, $J = 3.5, 2.5$ Hz, 2 H), 3.21 (dd,

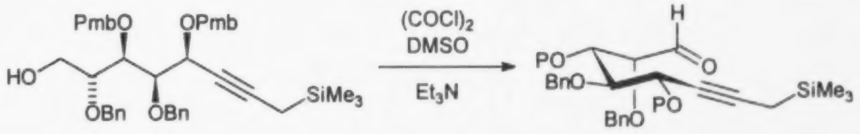
J = 11, 5 Hz, 1 H), 3.61 (dd, J = 11, 3 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.80-3.85 (m, 1 H), 3.98 (dd, J = 8, 3 Hz, 1 H), 4.25 (d, J = 12 Hz, 1 H), 4.27 (dd, J = 8, 3.5 Hz, 1 H), 4.32 (d, J = 10.5 Hz, 1 H), 4.45-4.54 (m, 4 H), 4.69 (d, J = 12 Hz, 1 H), 4.77 (d, J = 11 Hz, 1 H), 4.91 (d, J = 11.5 Hz, 1 H), 6.65-6.69 (m, 2 H), 6.76-6.82 (m, 2 H), 6.82-6.87 (m, 2 H), 7.13-7.32 (br m, 21 H), 7.41-7.49 (m, 6 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -1.80(q'), 7.39 (t'), 55.17 (q', we assume two signals are coincident at 55.17), 62.74 (t'), 70.53 (t'), 71.80 (t'), 71.83 (d'), 74.29 (t'), 74.63 (t'), 75.94 (s'), 78.48 (d'), 78.74 (d'), 81.68 (d'), 86.60 (s'), 86.77 (s'), 113.37 (d'), 113.70 (d'), 126.85 (d'), 127.02 (d'), 127.11 (d'), 127.16 (d'), 127.71 (d', we assume two signals are coincident at 127.71), 128.00 (d'), 128.18 (d'), 128.87 (d'), 129.66 (d'), 129.78 (d'), 130.15 (s'), 130.85 (s'), 138.85 (s'), 139.34 (s'), 144.15 (s'), 158.91 (s'), 159.13 (s'). Anal. Calcd for $C_{60}H_{64}O_7Si$: C, 77.89; H, 6.97. Found: C, 77.81; H, 7.23.

4,6-Di-*O*-benzyl-1,2-dideoxy-di-3,5-di-*O*-*p*-methoxybenzyl-1-methyltrimethylsilyl-D-*gluco*-1-heptynitol (115).



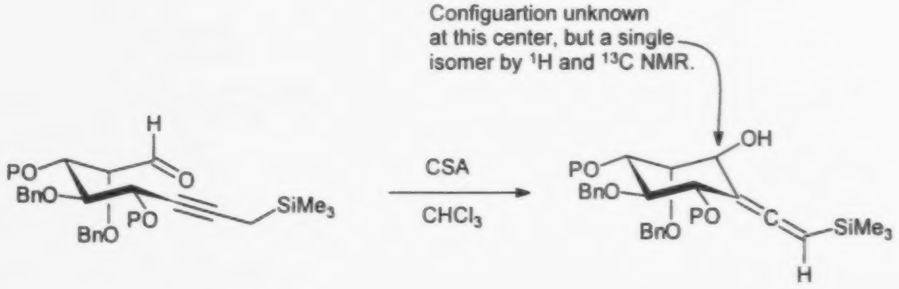
CSA (2 mg, 0.0086 mmol) was added in one portion to a stirred solution of **114** (185.6 mg, 0.2006 mmol) in 2:1 CH_2Cl_2:MeOH (18 mL) at room temperature. The resulting solution was stirred for 18 h, quenched with Et_3N (1 mL, 7.17 mmol), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 21 cm), using 20% EtOAc-hexane, gave **115** (120.3 mg, 89%) as a pure [^{1}H NMR (400 MHz)], oil: $[\alpha]_D$ = + 37.59° (c = 0.032, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3492 (br), 3088, 3063, 3031, 3002, 2954, 2934, 2907, 2871, 2836, 2212, 1732, 1612, 1586 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.15 (s, 9 H), 1.55 (d, J = 2.5 Hz, 2 H), 2.09 (dd, J = 7.5, 4 Hz, 1 H, exchangeable), 3.66-3.89 (br m, including s at δ 3.79 and 3.80, 12 H), 4.15 (dd, J = 7, 4 Hz, 1 H), 4.25 (d, J = 12 Hz, 1 H), 4.43-4.52 (m, 3 H), 4.57 (d, J = 12 Hz, 1 H), 4.66 (s, 2 H), 4.80 (d, J = 11.5 Hz, 1 H), 4.95 (d, J = 11.5 Hz, 1 H), 6.78-6.88 (br m, 4 H), 7.15-7.36 (br m, 14 H); ^{13}C NMR APT (CDCl$_3$, 100.6 MHz) δ -1.82 (q'), 7.39 (t'), 55.23 (q', we assume two signals are coincident at 55.23), 60.36 (t'), 70.57 (t'), 71.25 (t'), 71.59 (d'), 74.62 (t'), 74.89 (t'), 75.46 (s'), 79.05 (d'), 79.08 (d'), 81.49 (d'), 87.01 (s'), 113.66 (d'), 113.75 (d'), 127.35 (d'), 127.49 (d'), 127.62 (d'), 128.00 (d'), 128.17 (d'), 128.38 (d'), 129.74 (d', we assume two signals are coincident at 129.74), 130.00 (s'), 130.66 (s'), 136.28 (s'), 138.91 (s'), 159.15 (s', we assume two signals are coincident at 159.15). Anal. Calcd for C$_{41}$H$_{48}$O$_7$Si: C, 72.11; H, 7.38. Found: C, 72.23; H, 7.79.

2,4-Di-*O*-benzyl-6,7-dideoxy-3,5-di-*O*-*p*-methoxybenzyl-7-methyltrimethylsilyl-D-*gulo*-6-heptynal (116).



Dry DMSO (38 uL, 0.5318 mmol) was added to a stirred and cooled solution (-78 °C) solution of (COCl)$_2$ (35 ul, 0.5318 mmol) in CH$_2$Cl$_2$ (10 mL). After 20 min, alcohol **115** (90.8 mg, 0.1330 mmol) in CH$_2$Cl$_2$ (3 mL plus1 mL as a rinse) was added via cannula. After 30 min, Et$_3$N (0.15 mL, 1.064 mmol) was added and, after a further 30 min, the cold bath was removed and the solution was stirred for 3 h. The mixture was diluted with water (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using EtOAc-hexane mixtures (8 to 15% EtOAc) gave **116** (81.7 mg, 90%) as a pure [^{1}H NMR (400 MHz)], oil: $[\alpha]_D = -35.48°$ (c = 0.033 CH_2Cl_2); FT-IR ($CDCl_3$ cast) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 9 H), 1.56 (d, *J* = 2.5 Hz, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.83 (dd, *J* = 8, 4.5 Hz, 1 H), 4.03 (dd, *J* = 5, 2 Hz, 1 H), 4.21-4.27 (m,2 H), 4.40-4.59 (br m, 6 H), 4.76 (d, *J* = 11 Hz, 1 H). 4.89 (d, *J* = 11.5 Hz, 1 H), 6.77-6.86 (m, 4 H), 7.15 (d, *J* = 9 Hz, 2 H), 7.19-7.34 (br m, 12 H), 9.64 (d, J = 2 Hz, 1 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -1.61 (q'), 7.37 (t'), 55.25 (q', we assume two signals are coincident at 55.25), 70.59 (t'), 71.33 (d'), 72.29 (t'), 74.23 (t'), 74.99 (t'), 75.23 (s'), 80.40 (d'), 81.47 (d'), 83.88 (d'), 86.98 (s'), 113.66 (d'), 113.78 (d'), 127.56 (d'), 127.79 (d'), 127.84 (d'), 128.26 (d'), 128.40 (d'), 129.77 (d', we assume two signals are coincident at 129.77), 129.90 (d'), 129.99 (s'), 130.13 (s'), 137.52 (s'), 138.50 (s'), 159.28 (s', we assume two signals are coincident at 159.28), 201.34 (d'). Anal. Calcd for $C_{41}H_{48}O_7Si$: C, 72.32; H, 7.11.

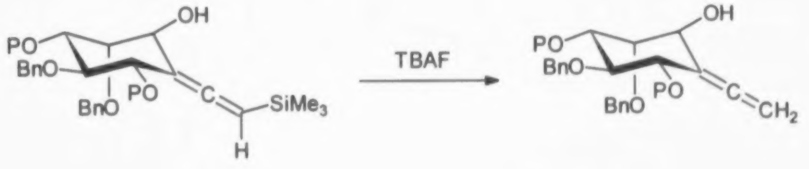
4-Deoxy-2,6-di-*O*-benzyl-1,5-di-*O*-*p*-methoxybenzyl-4-(2'-trimethylsilyl)-vinylidene-D-myo-4-inosose (117).



Configuartion unknown at this center, but a single isomer by ^{1}H and ^{13}C NMR.

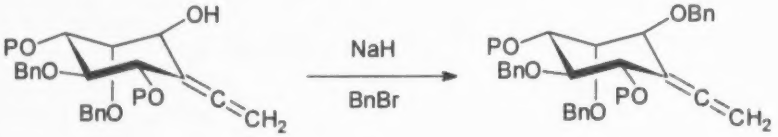
CSA (10 mg) was added to a stirred solution of **116** (161.0 mg, 0.2364 mmol) in $CHCl_3$ (20 mL) and the resulting solution stirred at room temperature for 12 h. At this point no starting material remained (TLC, silica 30% EtOAc-hexane) and the reaction was quenched by the addition Et_3N (1 mL). The solution was evaporated and flash chromatography of the residue over silica gel (3 x 29 cm), using EtOAc-hexane mixtures (10 to 25% EtOAc), gave **117** (135.4 mg, 84%) as a pure [^{1}H NMR (400 MHz)], gummy solid; $[\alpha]_D$ = - 4.76° (c = 0.0085, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3441, 3062, 3030, 3000, 2954, 2854, 1947, 1730, 1612, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (d, J = 2.5 Hz, 1 H, exchangeable), 3.68 (dd, J = 6.5, 3.0 Hz, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.82 (dd, J = 6.5, 3.0 Hz, 1 H), 3.91 (t, J = 5.5 Hz, 1 H), 4.49-4.70 (br m, 11 H), 5.80 (t, J = 2.5 Hz, 1 H), 6.72-6.80 (m, 4 H), 7.15-7.33 (m, 14 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ -0.83(q'), 55.26 (q', we assume two signals are coincident at 55.26), 67.25 (d'), 71.29 (t'), 72.14 (t'), 72.19 (t'), 73.79 (t'), 77.34 (d'), 79.33 (d'), 79.43 (d'), 86.46 (d'), 95.44 (s'), 86.59 (s'), 113.62 (d'), 127.52 (d'), 127.83 (d', we assume two signals are coincident at 127.83), 128.27 (d'), 128.31 (d'), 129.27 (d'), 129.43 (d',), 130.77 (d'), 130.80 (d'), 138.60 (d'), 138.64 (d'), 159.05 (s'). Anal. Calcd for $C_{41}H_{48}O_7Si$: C, 72.32; H, 7.11. Found: C, 72.25; H, 7.11.

4-Deoxy-2,6-di-*O*-benzyl-1,5-di-*O*-*p*-methoxybenzyl-4-vinylidene-D-myo-4-inosose (118).



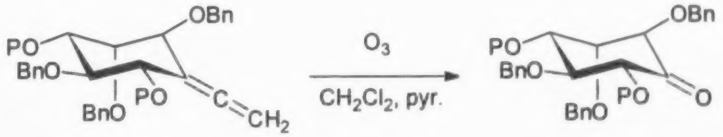
TBAF (0.153 mL, 1M solution in THF, 0.153 mmol) was added dropwise over 10 sec to a stirred solution of TFA (11.8 μL, 0.153 umol) and **117** (52.1 mg, 76.51 μmol) in THF (20 mL). The solution was stirred at room tempertaure for 3 h diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 28 cm), using EtOAc-hexane mixtures (20 to 25% EtOAc, (note compound comes off the column very slowly)), gave **118** (41.3 mg, 90%) as a pure [^{1}H NMR (400 MHz)], oil: $[\alpha]_D = 19.27°$ (c = 0.0123, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 1 H, exchangeable), 3.80 (dd, $J = 5.5, 3.0$ Hz, 1 H), 3.85 (s, 6 H), 3.92 (dd, $J = 7.0, 3.0$ Hz, 1 H), 4.01 (t, $J = 7.0$ Hz, 1 H), 4.27 (p, $J = 2.2$ Hz, 1 H), 4.49-4.80 (m, 7 H), 5.08 (qt, $J = 11, 2.5$ Hz, 2 H), 6.81-6.90 (m, 4 H), 7.25-7.40 (m, 14 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 55.28 (q', we assume that two signals are coincident at 55.28), 68.64 (d'), 71.79 (t'), 72.29 (t'), 72.34 (t'), 74.19 (t'), 77.56 (d'), 78.51 (t'), 79.07 (d'), 79.83 (d'), 101.77 (s'), 113.68 (s, we assume that two signals are coincident at 113.68), 127.57 (d'), 127.74 (d'), 127.84 (d'), 128.33 (d'), 129.45 (d'), 129.50 (d'), 130.56 (s'), 130.78 (s'), 138.51 (s'), 138.76 (s'), 159.11 (s, we assume that two signals are coincident at 159.11), 205.89 (s'). Anal. Calcd for $C_{38}H_{40}O_7$: C, 74.97; H, 6.86. Found: C, 74.97; H, 6.62.

4-Deoxy-2,3,6-tri-*O*-benzyl-1,5-di-*O*-*p*-methoxybenzyl-4-vinylidene-D-myo-4-inosose (123).



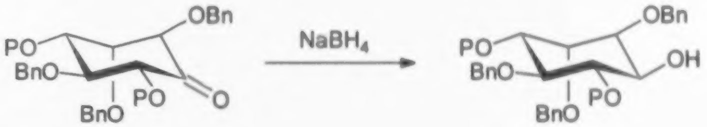
NaH (12 mg, 60% dispersion in oil, 0.300 mmol) was added in one portion to a stirred and cold (0°C) solution of **118** in THF (10 mL) and the resulting mixture was stirred for 15 min. Benzyl bromide (0.2 mL, 1.6 mmol) was added in one protion and the solution was refluxed for 12 h. The solution was then cooled, quenched with MeOH (2 mL), diluted with brine (10 mL) and extracted with Et_2O (4 x 10 mL). The combined ethereal extracts were dried and evaporated. Flash chromatography of the residue over silica gel (3 x 29 cm), using EtOAc-hexane mixtures (10 to 20% EtOAc), gave **109** (390.6 mg, 82%) as a pure [^{1}H NMR (400 MHz)], gummy solid; $[\alpha]_D = +$ 12.96° (c = 0.0054, $CHCl_3$); FT-IR (CH_2Cl_2 cast) 3029, 3002, 2909, 2864, 2835, 1961, 1611, 1585, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (s, 3 H), 3.76-3.83 (m, including s at 3.78, 8 H), 3.95 (t, J = 9.0 Hz, 1 H), 4.02 (t, J = 4.5 Hz, 1 H), 4.06 (d, J = 3.5 Hz, 1 H), 4.19 (d, J = 12 Hz, 1 H), 4.38 (d, J = 12 Hz, 1 H), 4.50-4.60 (m, 3 H), 4.61-4.69 (m, 3 H), 4.73-4.81 (m, 2 H), 4.84-4.93 (m, 2 H), 6.80 (t, J = 9 Hz, 4 H), 7.12-7.19 (m, 2 H), 7.20-7.35 (br m, 17 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) 55.29 (q', we assume two signals are coincident at 55.29), 70.11 (t'), 72.35 (d'), 72.94 (t'), 73.35 (t'), 75.84 (t'), 76.58 (d'), 77.80 (s'), 78.01 (d'), 79.78 (s'), 82.87 (s'), 99.49 (t'), 113.70 (d', we assume two signals are coincident at 113.70), 127.39 (d'), 127.56 (d'), 127.63 (d'), 128.16 (d'), 128.22 (d'), 128.27 (d'), 128.34 (d'), 129.43 (d'), 129.95 (d'), 130.54 (d'),131.10 (d'), 137.96 (s'), 138.67 (s'), 139.32 (s'), 159.14 (s'), 159.28 (s'), 206.50 (s'). Anal. Calcd for $C_{45}H_{46}O_7$: C, 77.34; H, 6.64. Found: 77.14; H, 6.85.

2,3,6-Tri-*O*-Benzyl-1,5-di-*O*-*p*-methoxybenzyl-D-myo-4-inosose (125).



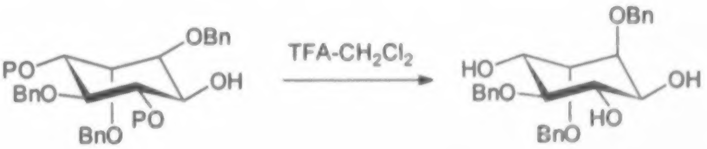
Ozone (pre-cooled to -78°C) was bubbled into a stirred and cold solution (-78° C) of **123** (33.0 mg, 47.22 mmol) in CH_2Cl_2 (10 mL) and pyridine (0.5 mL) until a permanent purple color was generated (ca. 3 min). The solution was stirred for 5 min and then argon was bubbled through the cold solution until the purple color disappeared. The cold bath was removed and the solution allowed to attain room temperature (ca. 3 h) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 29 cm), using EtOAc-hexane mixtures (8% to 20% EtOAc), gave **125** (22.4 mg, 70%) as a pure [^1H NMR (400 MHz)], oil: $[\alpha]_D = + 8.80°$ (c = 0.0083, CH_2Cl_2)FT-IR (CH_2Cl_2 cast) 3062, 3030, 3004, 2924, 2867, 2836, 1739, 1611, 1585, 1513, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.74 (s, 3 H), 3.76-3.83 (m, including singlet at 3.78, 8 H), 3.95 (t, J = 9.0 Hz, 1 H), 4.02 (t, J = 4.5 Hz, 1 H), 4.06 (d, J = 3.5 Hz, 1 H), 4.19 (d, J = 12 Hz, 1 H), 4.38 (d, J = 12 Hz, 1 H), 4.50-4.60 (m, 3 H), 4.61-4.69 (m, 3 H), 4.73-4.81 (m, 2 H), 4.84-4.93 (m, 2 H), 6.80 (t, J = 9 Hz, 4 H), 7.12-7.19 (m, 2 H), 7.20-7.35 (br m, 17 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) 55.23 (q'), 55.26 (q'), 72.48 (t'), 72.66 (t'), 73.10 (t'), 73.27 (t'), 75.05 (d'), 75.78 (t'), 78.96 (d'), 81.04 (d'), 81.92 (d'), 82.70 (d'), 113.76 (d', we assume two signals are coincident at 113.76), 127.61 (d'), 127.71 (d'), 127.82 (d'), 127.94 (d'), 128.15 (d'), 128.32 (d'), 128.49 (d'), 129.48 (d'), 129.77 (d'), 129.93 (d'), 130.48 (d'), 136.55 (s'), 137.63 (s'), 138.64 (s'), 159.23 (s'), 159.37 (s'), 204.87 (s'). Anal. Calcd for $C_{43}H_{44}O_8$: C, 74.98; H, 6.44.

2,3,6-tri-*O*-benzyl-1,5-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol (126).



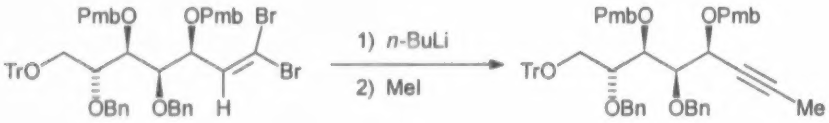
$NaBH_4$ (10 mg, 26.43 umol) was added in one portion to a cool (-20°C) solution of **125** in THF-MeOH (2 mL-6 mL). The resulting solution was stirred for 30 min at which point the cold bath was removed and stirring was continued for an additional 30 min. The reaction was quenched with 10% aqueous HCl (3 mL), diluted with water (5 mL), and extracted with Et_2O (3 x 10 mL). The combined ethereal extracts were washed with brine (1 x 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.0 x 23 cm), using EtOAc-hexane mixtures (20% to 30% EtOAc), gave **126** (7.5 mg, 87%) as a pure [^{1}H NMR (400 MHz)], oil: $[\alpha]_D = +9.28°$ (c = 0.0042, CH_2Cl_2)FT-IR (CH_2Cl_2 cast) 3491 (broad), 3062, 3030, 3003, 2931, 2868, 2835, 1611, 1585, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 1 H), 3.68 (dd, J = 9.0, 4 Hz, 1 H), 3.82-3.71 (m, 9 H), 3.93 (br s, 1 H), 4.50 (t, J = 12 Hz, 1 H), 4.26-4.33 (m, 2 H), 4.70-4.45 (m, 5 H), 4.89-4.73 (m, 3 H), 6.76-6.84 (m, 4 H), 7.05-7.10 (m, 2 H), 7.18-7.35 (m, 17 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) 55.27 (q' we assume two signals are coincident at 55.27), 70.23 (d'), 72.32 (t'), 72.50 (t'), 73.26 (t'), 74.09 (t'), 75.60 (t'), 77.35 (d'), 77.93 (d'), 78.63 (d'), 79.45 (d'), 79.82 (d'), 113.74 (d', we assume two signals are coincident at 113.74), 127.51 (d'), 127.84 (d'), 128.02 (d'), 128.12 (d'), 128.33 (d'), 128.41 (d'), 128.48 (d'), 129.54 (d'), 129.72 (d'), 130.71 (s'), 130.76 (s'), 137.46 (s'), 137.72 (s'), 139.03 (s'), 159.21 (s' we assume two signals are coincident at 159.21).

3-*epi*-2,3,6-tri-*O*-benzyl-D-*myo*-inositol (127).



TFA (3 drops) was added in one portion to a solution of **126** (12.5 mg, 18.09 μ mol) in CH_2Cl_2 (8 mL) and the solution was stirred open to the atmosphere at ambient temperature for 30 min. The solution was quenched with saturated NaHCO3 (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried and evaporated. Flash chromatography of the residue over silica gel (1.0 x 23 cm), using EtOAc-hexane mixtures (40% to 60% EtOAc), gave **127** (6.3 mg, 77%) as a pure [^{1}H NMR (400 MHz)], oil whose ^{1}H NMR (400 MHz) did not match that of the literature ^{1}H NMR for the known 2,3,6-tri-*O*-benzyl-D-*myo*-inositol. We therefore assign the structure of **127** as shown above.

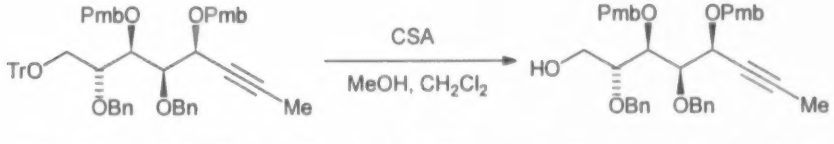
4,6-Di-*O*-benzyl-1,2-dideoxy-3,5-di-*O*-*p*-methoxybenzyl-1-methyl-7-*O*-trityl-D-*gluco*-1-heptynitol (109).



n-BuLi (0.80 mL, 1.6M in hexane, 1.277 mmol) was added over 45 sec to a stirred and cooled (-78°C) solution of dibromide **105** (554.4 mg, 0.5551 mmol) in THF (40 mL). The resulting solution was stirred at -78°C for 1 h, at which point the cold bath was removed and stirring was continued for 1.3 h. MeI (104.0 uL, 1.665 mmol) was then added in one portion by syringe and stirring was continued for 3 h at room tempertaure. The solution was diluted with Et_2O (30 mL), and washed with brine (1 x 10 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined ethereal extracts were dried and evaporated. Flash chromatography of the residue over silica gel (3 x 29 cm), using EtOAc-hexane mixtures (10 to 20% EtOAc), gave **109** (390.6 mg, 82%) as a pure [^{1}H NMR (400 MHz)], gummy solid; $[\alpha]_D$ = +

23.7° (c = 0.0196, CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 2932, 2917, 2870, 1612, 1513, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (d, *J* = 2 Hz, 3 H), 3.25 (dd, *J* = 11, 5 Hz, 1 H), 3.68 (dd, *J* = 11, 3 Hz, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 3.84-3.90 (m, 1 H), 4.06 (dd, *J* = 8, 3 Hz, 1 H), 4.32 (d, *J* = 12 Hz, 1 H), 4.35-4.45 (m, 2 H), 4.49-4.59 (m, 4 H), 4.75 (d, *J* = 12 Hz, 1 H), 4.81 (d, *J* = 12 Hz, 1 H), 4.95 (d, *J* = 12 Hz, 1 H), 6.73 (d, *J* = 9 Hz, 2 H), 6.83 (d, *J* = 9 Hz, 2 H), 6.90 (d, *J* = 9 Hz, 2 H), 7.18-7.39 (br m, 22 H), 7.45-7.55 (m, 5 H); ^{13}C NMR APT ($CDCl_3$, 100.6 MHz) δ 3.87(q'), 55.25 (q', we assume two signals are coincident at 55.25), 62.53 (t'), 70.77 (t'), 71.66 (d'), 71.87 (t'), 74.14 (t'), 74.66 (t'), 76.48 (s'), 78.48 (d'), 81.42 (d'), 84.29 (s'), 86.59 (s'), 113.41 (d'), 113.71 (d'), 126.91 (d'), 127.10 (d'), 127.22 (d'), 127.25 (d'), 127.75 (d', we assume two signals are coincident at 127.75), 128.04 (d'), 128.25 (d'), 128.89 (d'), 129.76 (d'), 129.78 (d'), 130.07 (s'), 130.84 (s'), 138.76 (s'), 139.25 (s'), 144.15 (s'), 158.96 (s'), 159.16 (s'). Anal. Calcd for $C_{57}H_{56}O_7$: C, 80.25; H, 6.62. Found: C, 80.06; H, 6.67.

4,6-Di-*O*-benzyl-1,2-dideoxy-3,5-di-*O*-*p*-methoxybenzyl-1-methyl-D-*gluco*-1-heptynitol (110).



CSA (1 mg, 0.0043 mmol) was added in one portion to a stirred solution of **109** (185.6 mg, 0.2006 mmol) in 2:1 CH_2Cl_2:MeOH (12 mL) at room temperature. The resulting solution was stirred for 18 h, quenched with Et_3N (1 mL, 7.17 mmol), and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using [illegible]OAc-hexane mixtures (10 to 20% EtOAc), gave **110** (59.2 mg, 80%) as a pure [^1H NMR (400 MHz)], oil: $[\alpha]_D$ = + 32.5 ° (c = 0.0353,CH_2Cl_2); FT-IR (CH_2Cl_2 cast) 3471 (br), 3062, 3030, 3002, 2932, 2917, 2868, 2836, 1612, 1585 cm⁻